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FURTHER OBSERVATIONS ON RAT LEPROSY.

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THE problems of infection and dissemination of rat leprosy have been detailed in a previous paper.[1] True infections of rabbits, guinea-pigs and kittens were not produced by subcutaneous inoculation. Lesions in the rabbits produced by subcutaneous inoculation were hard, encapsulated and non-vascular, and did not disappear by absorption; in the other animals the lesions were soft, and all disappeared by absorption. In these animals skin invasion by organisms was a feature; but the organisms always gradually disappeared, even after repeated inunctions. Rats, on the other hand, by superinfection with organisms of fæcal, urinary or primary ulcer origin showed more permanency of tenure, associated eventually with intracellularity of the organisms and the development of lepromata. Bush rats from Oro Bay, New Guinea, (six) and from Port Moresby, Papua (five), proved to be entirely free from rat leprosy organisms. One specimen of *Rattus norvegicus* and one *Rattus rattus* from Sydney showed light infections; in the former organisms were found in the axillary and cervical glands as well as in the ear and tail, while in the latter organisms were found in the preputial glands only.

A parallelism between human and rat leprosy has been suggested by me in a second paper.[2] Infection of rats having been accomplished by organisms from the excreta of affected humans and infected rats, the probability that dissemination is along similar lines in both cases is suggested.

In the above-mentioned papers the daily elimination of leprosy organisms in the excreta of affected humans and rats has been estimated by the Breed bacteria count. It has been shown that the mucosa of the stomach of heavily infected rats may be partially of completely destroyed, and that organisms stored dry for over two years are still viable and capable of invading the skin.

Simulation of Natural Infection.

The light natural infections of wild rats and the infection of laboratory rats by inunctions with organisms from excreta suggested an attempt to simulate natural conditions. For this purpose a two-compartment box was constructed; fresh fæcal organisms were mixed with soil and water in the small compartment, in which the laboratory animals were confined for portion of the day. Before examination the killed animals were thoroughly washed to eliminate external organisms; 33 portions of the skin and organs were examined microscopically by means of stained smears.

EXPERIMENT LIV: Eight rats (two with vitamin B_2 deficiency) and four mice were introduced into the box. On the fifteenth day an emulsion of dried fæcal organisms was mixed with the wet soil; after this, on alternate days to the seventy-first day, fresh fæcal organisms were added to and well mixed with the soil. On the eighteenth day, a mouse was killed; organisms were noted in smears of the skin of the tail and abdomen, also in the axillary and inguinal glands. On the twenty-fifth day, another mouse was killed; organisms were noted in smears of the skin at the tail, testes and breast, in the preputial gland and in an ulcer of the skin on the back. On the twenty-sixth day a rat deficient in vitamin B_2 was killed; organisms were noted in smears of the skin at the tail, ear and back, and the fore-paws and hind-paws; single organisms were found in polymorphonuclear leucocytes from the ear and paw. On the thirty-

[1] Unfortunately, an error crept into the legends to figures VII to IX in this paper; to correct this, substitute "primary ulcer inunction" for "primary inunction".

fourth day a mouse died; four pustular lesions were noted, one containing acid-fast organisms—these were also noted in smears of the skin at the tail, genitals, and fore-paws and hind-paws; globi (non-nucleated cells) containing up to 500 organisms were noted in the tail and paw smears; the axillary glands and abdominal muscle also contained loose organisms. On the sixty-fourth day a mouse was killed; organisms were noted in smears of skin at the fore-paws and hind-paws, and in the inguinal and cervical glands.

On the seventy-second day two rats were segregated from soil contact and placed in the cage of experiment LVI.

On the eighty-third day a rat was killed; organisms were noted in smears of skin at the tail, genitals, rump and hind-paw and in the suprarenal glands. On the 153rd day a rat was killed; organisms were noted in smears of skin at the tail and abdomen only. On the 160th day a rat was killed; examination of smears from all portions gave completely negative results. On the 162nd day, the second rat which was deficient in vitamin B_2, now normal, was killed; examination of smears from all portions again gave negative results.

From these results it appeared obvious that bacillary invasion of the animals had ceased, and this suggested that the viability of the organisms had probably been affected by reactive changes in the wet soil mixture. Consequently the invasive quality of the organisms was tested by an inunction on the remaining rat.

On the 163rd day, inunction with the soil mixture was carried out for two hours on the scarified skin of the abdomen; the area was immediately washed, and examination of skin smears from various parts of the area gave entirely negative results, although the soil used contained numerous bacilli. On the 164th day rat was killed; examination of smears from the well cleansed area of inunction again gave negative results; this finding applied also to the usual parts of the skin and the various organs which in other animals had been regularly examined.

The above results indicated that a building-up of infection occurred during the first few weeks of contact with the infected soil. Thereafter there appeared to be evidence of an elimination of the organisms from the body of the animal. Further to test the viability or invasiveness of the organisms in the soil, it was decided to carry out the following experiment.

EXPERIMENT LVII: Five mice were confined daily to the infected soil; after thirty-two days all the mice were killed and washed to remove external organisms. No organisms were found in the usual skin and organ smears.

It was therefore considered that the viability of the organisms had been destroyed, probably by the addition of the water, which had caused the mixture to become sour.

Removal from Contact with Infected Soil.

Since animals which had been held in contact with contaminated soil were infected, it was decided to note whether intensification of infection took place after segregation of the animals from the contaminated soil. Two rats from Experiment LIV (normal) and one rat and one mouse from Experiment LV (after four injections of carbolized organisms) were transferred from the soil to Experiment LVI, seventy-two days from the original starting time.

On the 148th day (seventy-sixth from separation), an injected mouse was killed; organisms were noted in smears of the skin at the abdomen; they were also found in smears of the lung and bladder and in muscle of the foreleg, breast and abdomen. On the 162nd day an injected rat was killed; organisms were noted in smears of the skin at the breast and abdomen, and in inguinal and cervical glands; they were also plentiful in the breast muscle. On the 162nd day a non-injected rat was killed; examination of smears from the usual places gave completely negative results. On the 167th day, the remaining non-injected rat was transferred to Experiment LVIII with an injected rat, to test whether the animals had been immunized. A normal rat was added as a control, and all were treated with viable fæcal organisms by inunctions and skin-slit inoculations.

Intracellularity and Early Leucocyte Mobilization.

Apparently, before true leprotic intracellularity can occur, local resistance must be broken down; this, according to my experience, can be accomplished by viable organisms only. The local breakdown is followed by extracellular multiplication associated with an inflammatory mobilization of leucocytes which are invaded by organisms. Muir[40] puts it this way: "Apart from lepra fever, the ordinary signs and symptoms of leprosy are due chiefly to the local response of cells to bacilli in their neighbourhood." Prior to this, the organisms may be loose, in bundles, or in the characteristic globi formation; a similar picture may later be observed in fæcal smears. Skin smears from rats are frequently similar in microscopic appearance to that shown by Rogers and Muir's Figure XI.[40] Although intracellularity of the polymorphonuclear cells (microphages) attains maximum proportions, the lymphocytes and mononuclear cells (macrophages) are usually invaded by only a few organisms. There is evidence of intracellular multiplication in the polymorphonuclear cells, the organisms varying from Hoffmann granules to long rod forms. Maximum intracellularity is associated with true leprotic virulence and lesions; these vary in size and appearance, apparently according to the degree of viability and number of the invading organisms at the time that resistance has been broken down. When leproma or other leprosy organisms are inoculated subcutaneously, they result in a primary lesion which may become absorbed or may ulcerate. When large numbers are given by inoculation, this procedure is usually followed at a later date by a secondary lesion or true leproma. Repeated invasion of scarified or intact skin by leproma organisms does not apparently result in intracellularity of organisms or in lesions even after prolonged treatment; however, organisms so given appear to be capable of partially breaking down the local resistance of the animal. Continuation of inunction with organisms from the excreta or from primary ulcers results in the production of intracellularity of organisms and in lesions. These results suggest a difference in the viability of organisms from different sources—namely, lower viability in those from lepromata and excreta after long periods of drying, and higher viability in fresh organisms from the excreta and from primary ulcers. In some experiments early invasion of the microphages by one to three bacilli occurs, but there is no continuity of intracellularity in these early stages. When a leproma appears, the microphages frequently become heavily filled with parasites and show variability of the nuclei, which may be forced into different shapes or clumped eccentrically by the organisms; sometimes they may be split into various pieces of smaller or larger size, or they may be completely eliminated. Organisms have also been recorded in other types of cells, one, a non-nucleated cell smaller than a small lymphocyte, the cytoplasm of which takes up the counterstain. Frequently encapsulation of single or multiple organisms may be noted; these bodies may attain a great size and contain some hundreds of organisms in various stages of division; the counterstain is ineffective in these bodies. It has been concluded that these bodies are the true globi and may be multiplication centres. (The word "globi" needs some clarification; it is apparently used for any of the intracellular aggregates.) Krakower and Gonzalez[41] also have noted the degenerative nuclear changes in the lepra cells, and suggest that wrinkling, infolding or finger-like processes may be present or that the nuclei may be completely lysed. The cells retain their outline and contain masses of packed bacilli in a presumably non-stainable liquid medium. Krakower and Gonzalez consider that necrotic areas are infiltrated or overrun peripherally by polymorphonuclear cells, and that young histiocytes containing bacilli and perivascular aggregates of lymphocytes are associated with rat lepromata.

The following observations were carried out to test whether maximum intracellularity could be induced by prior, simultaneous or subsequent mobilization of leucocytes and an early infection by organisms. Hot towels were used prior to the inunctions, and a weak solution of ammonia was used prior to, with or subsequent to the inunctions. Injections of a 25% peptone solution were given intradermally after inunction with organisms, and subcutaneously or intrapleurally either with or followed

by injections of organisms. Notes on these methods will be found in the details of various experiments.

EXPERIMENT XLVIII: A rabbit was inoculated subcutaneously with three millilitres and into the pleural cavity with seven millilitres of 25% peptone solution mixed with rat leproma organisms. The rabbit was killed next day, and examination revealed absorption of the subcutaneously injected material and no organisms in a washing of the site. The pleural cavity yielded 15 millilitres of fluid containing polymorphonuclear and other cells; no organisms were noted.

EXPERIMENT L: The 25% peptone solution mixed with fæcal organisms (one to three fields) was inoculated in quantities of 0·5 millilitre into the pleural cavities of ten mice. The results were as follow. The first mouse died immediately after the injection; it was not examined. After five hours, the second mouse was dead; in the 2·25 millilitres of pleural fluid, examination of smears revealed only loose organisms (one to five fields). After twenty-three hours, the third, fourth, fifth and sixth mice were dead. In the fourth mouse no pleural fluid was found; in the others 1·5 millilitres of fluid was present. In smears from the fourth and fifth mice no organisms were found; examination of smears from the other two mice revealed loose organisms. After thirty hours the seventh mouse was dead; no organisms were noted in smears of the 1·5 millilitres of pleural fluid. After forty-seven hours the eighth mouse was dead; very little pleural fluid was present and a cavity washing contained loose organisms. Polymorphonuclear cells contained one or two acid-fast organisms, others contained Wherry's Gram-positive diplococci. After fifty-two hours the ninth mouse was dead and no pleural fluid was present; the results of examination were similar to those obtained with the eighth mouse. After 120 hours the tenth mouse was killed. No pleural fluid was present, and no organisms were found in cavity washing smears. Organisms were not recovered from various organs, but Gram-positive diplococci were recorded in the inguinal gland and thymus.

EXPERIMENT LI: A rat was inoculated into the pleural cavity with 1·25 millilitres of 25% peptone solution. Next day 0·5 millilitre of a rat leproma emulsion was injected into the same place. After forty-eight hours the rat was killed. The pleural cavity was filled with fluid (not measured); no acid-fast organisms were found in smears. At fifty-one hours the cavity fluid was thoroughly mixed and smears were made and stained. Organisms were present loose, and in ones, twos and threes in polymorphonuclear leucocytes. At fifty-fours the cavity was again well mixed. Smears contained loose organisms, together with organisms in ones or twos in polymorphonuclear leucocytes.

In these observations there was no evidence of typical maximum intracellularity similar to that observed in leprotic lesions.

Premunity Reinfection or Immunity.

Like Marchoux, I have held that there is an acquired immunity in rat leprosy; further evidence appears in the following observations. The fact that organisms were eliminated from the body in Experiments LIV, LVI (*b*) and LVIII (*b*) is proof that a state of premunity can exist, the invading organisms being eliminated as they gain entrance by inunction. That this premune state may be followed by a more practical immunity is suggested by the final results obtained after extended treatment in Experiments XLVI and LVIII (*b*), in which obvious elimination of organisms occurred, even after skin-slit inoculation with heavy doses.

EXPERIMENT XLVI: A rat was inoculated subcutaneously at the hind leg with 0·3 millilitre of an emulsion of two years old dried fæces. No primary or secondary lesion resulted. On the fourteenth, twenty-fourth, twenty-eighth and fifty-seventh days, the rat was inoculated with 0·5 millilitre of its own hæmolyzed blood (one part in three parts of water); the first lesion ulcerated at thirteen days, but no organisms were found in it; the other lesions were absorbed. At the seventy-eighth day the rat was inoculated with hæmolyzed blood from rat number 47; a lesion two millimetres in diameter at four days was cut out, and examination of sections revealed typical acid-fast organisms. On the thirty-second, forty-fourth, fiftieth, fifty-seventh, sixty-fourth, seventy-eighth, eighty-sixth, 120th, 126th, 133rd and 148th days, the scarified abdomen was treated by inunction with emulsions of dry fæces; at 116 days the inunction emulsion contained a few drops of ammonia. Next day there was evidence of mobilization of polymorphonuclear and other cells, one of the former containing a single acid-fast organism. On the thirty-third, fifty-seventh, 127th and 139th days, organisms were noted in skin smears, an occasional single organism being found in polymorphonuclear cells. On the 153rd day, 0·3 millilitre of a leproma emulsion and a fæcal emulsion was inoculated subcutaneously at the right and left breast respectively. The lesion produced from the leproma was small, and it was absorbed; the fæcal lesion was larger; it ulcerated and was found to contain organisms on the fourth day. At 200 days the rat was killed, and no organisms were found in the usual skin and organ smears.

EXPERIMENT LII: A rat was inoculated with its own hæmolyzed heart blood; there was no evidence of a lesion. On the fifth day, inunction of the scarified abdomen with a fresh fæcal emulsion containing a few drops of ammonia was carried out; although next day an obvious cellular invasion was present, no organisms were noted in smears. On the twelfth, fifteenth, nineteenth, twenty-eighth and twenty-ninth days, inunction of the same scarified area was carried out, with emulsions of dry or fresh fæces. On the twelfth, thirteenth, nineteenth and twentieth days, loose organisms were present, and a single organism was found in a polymorphonuclear cell on the two last-mentioned days. On the thirty-fifth day, 0·5 millilitre of a leproma emulsion was inoculated subcutaneously; the resulting lesion was small and was absorbed early. At the forty-first day the rat was killed; no organisms were detected in any of the usual smears.

In Experiment LVIII the question was whether the invasion by organisms of, and the elimination of organisms from, the segregated animal from the normal simulation experiment, or from this experiment and from that in which carbolized bacilli were given also, had produced immunization of the animals.

Three rats were used: rat A (normal), rat B (from Experiment LVI—soil contact for seventy-two days, segregated from soil for ninety-five days) and rat C (from Experiment LV—four injections of carbolized bacilli, soil contact for 167 days). Early emulsions were made from dried fæces (up to three years old); they were mainly dried and reconstituted for each inunction; later emulsions were made with fresh fæces from rat C in Experiment LVIII. On the first, fifth, twelfth, nineteenth, twenty-eighth, thirty-fourth, fortieth, forty-seventh, sixty-first, sixty-eighth, seventy-seventh, eighty-third and eighty-fifth days, inunction of all three rats was carried out on the scarified abdomen. Inunction of rats A and B was carried out also on the eighty-ninth, ninety-fifth, 108th, 113th, 130th, 135th, 140th, 145th, 153rd, 160th, 167th, 168th, and 176th days. From the 135th day the fæces used were from rat C in this experiment; the fæces were recently passed and emulsified as required. On the fifty-fourth day, all rats were inoculated at the breast region by the skin-slit method with an emulsion of dried fæces. On the eighty-fifth day, rats A and B received another skin-slit inoculation with a similar emulsion. On the 135th and 153rd days, rats A and B received another inoculation with an emulsion of fresh fæces of rat C. On the eighty-ninth day, each rat was inoculated subcutaneously with its own hæmolyzed heart blood; the procedure was repeated with rats A and B on the 135th and 183rd days. Lesions in all cases were prominent. On the 183rd day rat B was accidentally killed during bleeding; this, because of the necessity for a comparison, prematurely finished the series. In rat A, organisms were found in skin smears (mainly from the abdominal region) on the fifth, twelfth, twentieth, sixty-second, seventy-fifth, eighty-third, eighty-ninth (globi), ninety-sixth, 108th, 118th, 124th, 127th, 128th, 132nd, 135th, 139th, 145th, 151st, 152nd, 158th, 159th, 161st, 166th and 174th days. On the 108th day the organisms were found in skin from the inguinal region and on the 118th day from the breast region; on the 161st day capsular globi were found and a bacillus in a mononuclear cell. On the 183rd day, an axillary gland washing contained numerous organisms. On the 187th day rat was killed for comparison with rat B. Organisms were found in fair numbers in smears from the following sites: the skin at the axillary region, abdomen and back—fewer organisms were found in smears from the fore-paws and hind-paws; the muscle at the front leg; glands at the inguinal and axillary regions; thymus, lung and spleen. In the bone marrow organisms and Hoffmann granules were present. Organisms were plentiful in the pancreas, and a few were found in the brain. Smears from a number of small ulcerative sores on the skin of the back contained a few bacilli. A small lesion from the last blood inoculation was broken up; examination of smears revealed a fair number of organisms in various stages of division, from Hoffmann granules to long rod forms.

There was definite evidence of a progressive infection in this animal. To judge from past experience, the abdominal and axillary regions of the skin would undoubtedly become lepromatous at an early date, and intracellular organisms would have appeared there.

In the case of rat B, organisms were found in skin smears from the abdominal or axillary regions on the following days: twentieth (some loose organisms and single organisms in mononuclear and polymorphonuclear cells), sixty-eighth, eighty-third, ninety-sixth, 118th, 123rd, 128th, 132nd, 135th, 139th, 145th, 151st, 152nd, 158th, 159th, 160th and 174th. The rat was killed by accident on the 183rd day.

Examination of various organs and of the usual skin sites revealed few organisms in the abdominal muscle and the skin of the back; there was a fair number of organisms in the pancreas and the inguinal glands. Besides these, there were a couple of small subcutaneous lesions arising from the later skin-slit inoculations, and on dissection these were found to contain a small number of typical acid-fast organisms.

Compared with the number of organisms used for inunction and skin-slit inoculation, those remaining in the body were in small numbers. It should also be remembered that thirty days prior to death the rat had received many millions of organisms by skin-slit inoculation, and had received inunction at the abdomen five times during the same period. Furthermore, in comparison with the number of organisms found in rat A, there appears to be evidence of elimination of organisms, which would certainly have been completed at an early date. Thus, from the evidence, it has been concluded that, under certain conditions, animals may become immunized against rat leprosy.

In rat C, on the twentieth day, cellular invasion of the abdominal skin by polymorphonuclear cells and some lymphocytes was apparent; no acid-fast organisms were noted, but some intracellular organisms were present in polymorphonuclear cells and some Gram-positive diplococci. On the thirty-fourth, fortieth, forty seventh, fifty-first, sixty-second, sixty-eighth and eighty-fourth days there appeared to be a progressive increase in the number of organisms in the abdominal skin from 11 to 169 per 50 fields. On the forty-seventh day a mononuclear cell and a polymorphonuclear cell each contained organisms. On the seventy-seventh day, the discrete and plentiful nodular lesions which had been observed in the subcutaneous tissue at the top of the breast were coalescing to form a lepromatous lesion. The nodules had resulted from the skin-slit inoculation on the fifty-fourth day. On the eighty-fourth day, in a skin smear of this region 161 organisms were counted to 10 fields. At this time a lesion one centimetre in diameter had appeared on the abdomen, and a smear from this contained 169 organisms to 50 fields. At fifty-one days, the abdominal skin, which had undergone a steady increase in the number of organisms present, was inoculated intradermally with 25% peptone solution. Next day smears of the injected area contained plenty of polymorphonuclear and mononuclear cells and lymphocytes, but no organisms; on the following day a small number of organisms were noted, but none were intracellular. The leproma at the top of the breast had obviously resulted from the skin-slit inoculation with dried (thirty-four months) fæcal organisms from the rat in Experiment IV, while the abdominal leproma had resulted from the repeated inunctions with the same type of organism. On the 107th and 126th days examination of fæcal smears gave negative results; on the 131st day a fæcal smear contained one organism to thirty fields. On the 133rd day a Breed count revealed one organism per field, or a daily elimination of 20,000,000 organisms. On the 140th day there were two organisms per field by Breed count, or a daily elimination of 40,000,000 organisms. By the 148th day the daily elimination had increased to 400,000,000 organisms. On the 154th day the abdominal and breast lesions had become ulcerative, while fæcal elimination had increased to 6,075,000,000 organisms per day. At 165 days the Breed count was similar to the previous count. On the 184th day the rat was killed and fixed whole.

From these results, it appeared evident that the carbolized organisms (inoculated in the first doses) were still viable, and with the assistance of the early invaders from the soil were capable of undermining the resistance of the animal. This is evidenced by the early appearance of lesions and intracellular organisms after inunctions and skin-slit inoculation.

Attempt at Immunization with Carbolized Organisms.

Immunization against rat leprosy has been attempted, but so far without success, unless the achievement of immunization was suggested by the total elimination of organisms from some of my laboratory animals. It was therefore decided to try simple carbolized bacillary emulsions instead of emulsions which had been sterilized by heat. This was done because it was considered that sterilization might alter the constitution of the bacillary protein, making it, as others have suggested, proof against the body fluids. There is evidence that such organisms after injection into animals have been found to survive for considerable periods. In the present series the carbolized organisms were injected simultaneously with invading organisms in Experiment LV or subsequent to infection as in Experiment XLVII.

EXPERIMENT XLVII: A rat was inoculated subcutaneously at the hind leg with 50,000,000 leproma organisms, which had been in the refrigerator for two days; no evidence of primary or secondary lesions resulted. On the fifty-third, sixty-ninth, ninetieth, ninety-seventh and 145th days injections of its own hæmolyzed blood produced lesions up to 1·5 millimetres in diameter, which were absorbed. On the 108th day, an injection of hæmolyzed blood of the rat from Experiment XLVI resulted in a small lesion. This ulcerated five days later and was found to contain organisms. On the seventy-third, eighty-fourth, ninetieth, ninety-seventh, 104th and 108th days, inunction on the non-scarified breast and the scarified abdomen was carried out with emulsions of dried fæces after two years' storage; the total number of organisms used was about 125,000,000. Skin smears contained loose organisms on the following days: seventy-sixth, ninety-seventh (single bacillus in a polymorphonuclear cell), 104th, 108th, 109th and 111th (a few globi). On the 108th day an inguinal gland washing contained organisms, and on the 119th day many cells were invaded by organisms. On the 123rd day an abdominal leproma was present, in which extensive invasion of polymorphonuclear cells was found, a few organisms being present in large lymphocytes. The breast organisms were mostly loose; this area was injected intradermally with 25% peptone solution, but this procedure did not accelerate any intracellular invasion by the organisms.

Because the original inoculation was at the hind leg, it is suggested that the ventral surface (breast and abdomen) lesions were entirely due to the inunctions with fæcal organisms. Since, according to observations, only a small percentage of organisms given by inunction invade the skin, and allowance of 5% or some 7,000,000 organisms was made.

On the 158th day, three circles of skin one centimetre in diameter from the breast, sternum and lower part of the abdomen were cut out, and each was found to contain many organisms. The emulsion of these three pieces gave a total Breed count of 60,000,000 organisms; the whole inunction area was about ten by three centimetres or 12·7 times greater than the three circular pieces of skin.

Therefore, an estimate of 762,000,000 organisms is given for the whole inunction area; since multiplication of the organisms had taken place between the 111th and 119th days, the calculations reveal an increase in organisms equal to 100 times in thirty-nine to forty-seven days. It is of interest to note that at about this time an examination of ten pieces of skin cut out from other than the inunction area revealed signs of organisms in only one; this was from the top of the head, and only one was noted after an extensive examination.

Since the ventral surface was now almost completely lepromatous, it was decided to try the effect of injections of an emulsion of carbolized organisms and carbolized saline solution. The emulsion was kept frozen between injections, which were given into the leproma, subcutaneously, intraperitoneally or intramuscularly on the 162nd, 196th, 205th, 208th, 217th and 240th days, when a total of 225,000,000 carbolized organisms had been given. Carbolized saline solution was also injected into the lepromata on the 230th and 240th days. The leproma injections in both cases resulted in localized hardening, which remained prominent for some time afterwards. On the 193rd day a Breed fæcal count revealed a daily elimination of some 3,000,000 organisms. On the 270th day fæcal elimination had attained daily some 4,000,000,000 organisms; urinary elimination of

organisms was about 5,000,000 per day. The rat at this stage was heavily infested by rat lice (*Polyplax spinulosus*). On the 287th day the rat died. The internal lesions of the body cavities were fairly widespread, the mucosa of the stomach being almost completely destroyed.

A comparison of the details of fæcal eliminations from start to finish in this experiment with those in Experiment LVIII (rat C) raises the question of the effectiveness of carbolized organisms in holding up the stomach infection and the resultant fæcal eliminations.

EXPERIMENT LV: Three piebald female rats and three male mice were each given four subcutaneous and/or intraperitoneal injections with carbolized organisms. The first two injections on the first and fifth days were given after refrigeration of the emulsion for two and seven days respectively; the other two injections on the nineteenth and twenty-sixth days were given after the emulsion had been kept frozen from the seventh day. The rats received a total of about 100,000,000 organisms and the mice half this number. The animals were kept in the box for emulation of natural infection with those of Experiment LIV. On the fourteenth day, one mouse, which was sickly, was killed. No organisms were found in the usual smears of skin and organs. On the seventy-second day, one rat and one mouse were transferred to Experiment LVI box, out of contact with the infected soil. On the eighty-third day another mouse was killed. Organisms were noted in the skin at the ear, tail, genitals, breast, abdomen, fore-paws and hind-paws, and also in the axillary, inguinal and suprarenal glands. They were plentiful in the liver, spleen and abdominal muscle. On the eighty-fourth day one rat was killed. Organisms were plentiful in breast skin, less so in the skin at the abdomen, tail, genitals and hind-paws. They were also present in the axillary, inguinal and cervical glands, and a few were noted in a smear of the stomach. On the 167th day, the remaining rat was transferred to the immunity test experiment (LVIII) as rat C for inunctions and skin-slit inoculation.

Discussion.

Experiment LIV was an attempt to emulate natural infection. There was an obvious building-up of infection in the animals; this was followed by a decline in the number of organisms, until at 160 days the animals had returned to a "negative" state—that is, all organisms had been completely eliminated. These results suggested that organisms in the soil mixture had lost their viability (proved later), probably owing to reactive changes caused by the addition of water. It was also considered that the elimination of organisms from the body might indicate an acquired immunity. The heavy dosing of organisms by skin-slit inoculation and inunction and the obvious elimination in rat B, Experiment LVIII, appear to prove that such an immunity may be produced. After injection with carbolized organisms and invasion of organisms from the soil in Experiment LV, there was retention of organisms during the whole experimental period; it was, of course, impossible to decide whether they were fæcal invaders or from the emulsion, but their appearance in some locations suggested that they were from the former source. The fact that lepromata appeared early in Experiment LVIII, rat C, from both skin-slit inoculation and the inunctions, suggested that many of the carbolized organisms were alive and had assisted in reducing the resistance of the animal. Experiment LIV is of some interest when viewed with the experimental inunctions with human excreta;[3] it appears to prove that my original idea that the viability of the organisms was reduced by inimical storage was sound. It will be noted also that some rat infections produced by both human and rat excreta organisms were similarly eliminated.

While fæcal organisms stored dry for some time are still viable and invasive, there is evidence that fresh excreta organisms may break down resistance more quickly and produce earlier intracellularity of organisms (which, in my opinion, is synonymous with virulence). Lesions in rats appear about the same time, being followed incidentally and invariably by a generalized disease. However, in different animals a variable time factor is associated with continued treatment with either type of emulsion. Loose organisms may occasionally be noted in the stomach and bladder smears of rats killed early; but permanency of infection of these organs apparently does not become obvious until maximum intracellularity of organisms, of leprotic proportions, is attained superficially.

From the time intracellularity of organisms and/or lepromata appear, to the time organisms appear in the urine or fæces, there elapses a period varying from sixty-one to one hundred and twenty-one days or more. While the genital organs and bladder do not appear to become seriously diseased, the stomach may show striking changes; from the cardiac end, the mucosa may eventually be destroyed to the pyloric constriction, but in my experience apparently the disease does not gain ground beyond the junction.

The multiplication figures of organisms in lepromata and their subsequent elimination from the stomach via the fæces are rather illuminating when taken from the viewpoint of the Breed bacteria count. Two or three examples to show this build-up and elimination of organisms will suffice. The actual tendency for increase in leproma organisms was noted soon after the final inunction with an emulsion of a primary ulcer. At eight days from the inunction, from the rat in Experiment IV, a Breed count of 18,000,000 per millilitre was obtained; as the actual leprotic area measured about four centimetres by four centimetres by 0·5 centimetre, the extent of multiplication can be appreciated. There was during the next few days a further increase in the number of organisms. Intracellularity or invasion of polymorphonuclear and other cells by organisms occurred about the twelfth day. The increase in the number of organisms in Experiment IV should be compared with the calculated increase in Experiment XLVII of the present series. In rat C, Experiment LVIII, the elimination of organisms from the stomach was most spectacular; on the first day they were noted the number was small, but weekly estimations revealed that at the end of the fourth week the daily elimination had reached 6,075,000,000, and many non-nucleated cells containing variable numbers of organisms were present.

The elimination of fæcal organisms supplies evidence also of the extent of localized multiplication in the stomach. Inoculation by the skin-slit and probing method had proved of considerable interest. In the early stages of infection the lesions so produced tend to be concentrated into a few subcutaneous nodules and to be absorbed early; a few may ulcerate through the skin. When infection has been built up somewhat, subsidence of the lesions is apparently much slower. But when resistance has been broken down, as in Experiment LVIII, rat C, there is evidence of multiple nodular lesions which eventually resolve to a thick lepromatous lesion. In this experiment an examination of skin smears of this lesion revealed 161 organisms in ten fields thirty days after the skin-slit inoculation. More work to check this aspect is required.

The early appearance of organisms in the muscle of the breast, abdomen and leg after inunction has also proved interesting; these sites may assume some importance as constituting storage bases for organisms which later, when local resistance has been broken down, may invade the skin. The finding of flecking and small lesions on the abdominal muscle and skin after intraperitoneal inoculation, as illustrated by Krakower and Gonzalez,[4] suggests that such a close connexion may be a possibility, especially in view of the finding in Experiment LVIII, rat C.

The rat leprosy investigations have been associated with attempts at the cultivation of organisms on various media. These, however, have so far been without success.

Summary.

1. Fæcal organisms have again been responsible for the infection of rats with leprosy.

2. In experiments simulating natural infection, rats and mice showed a building-up of organisms which was followed by their gradual complete elimination.

3. When removed from infected soil at seventy-two days, other rats also became free from leprosy organisms.

4. These results suggest the necessity of superinvasion by highly viable organisms for the production of lesions; they suggest also that viability of organisms can be lowered

or destroyed by reactive changes (souring) in a fæces-soil-water mixture.

5. When killed thirty-two days after their introduction to the emulation experiment box at 163 days from the start, five mice proved to be completely free from leprosy organisms; this indicates the destruction of the viability of the organisms.

6. The elimination of leprosy organisms from the body suggested an acquired immunity; this was apparently borne out by the results in Experiment LVIII (rat B).

7. Simple carbolization of rat leprosy organisms for two to seven days was not sufficient to destroy their viability. One rat injected with these and then treated with viable fæcal organisms responded with early lepromata and a generalized infection.

8. Mobilization of leucocytes associated with early infections with rat leprosy organisms did not respond with the development of maximum intracellularity. Apparently inflammatory mobilization conditions due to superficial multiplication of organisms are a necessity.

9. Infection of rats by rat leprosy is not enhanced by vitamin B_2 deficiency.

10. Fæcal organisms from leprous rats after three years' storage are comparatively intact and capable of invading the skin of rats and mice. Viability, however, appears to be somewhat lowered.

11. Muscular layers in rats and mice probably act as bases for storage of organisms in rat leprosy.

12. Light infections of rat leprosy are recorded in *Rattus norvegicus* and *Rattus rattus* in the Sydney region.

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References.

(1) J. W. Fielding: "Rat Leprosy: Observations and Transmission", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, 1945, page 473.
(2) J. W. Fielding: "Observations on Human Leprosy: Infection of Rats with Excreta Organisms", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, 1946, page 578.
(3) C. Krakower and L. M. Gonzales: "Mouse Leprosy", *Archives of Pathology*, Volume XXX, 1940, page 308.
(4) E. Muir: "Juvenile Leprosy", *International Journal of Leprosy*, Volume IV, 1936, page 45.
(5) L. Rogers and E. Muir: "Leprosy", Second Edition, 1940, page 252.

CLINICAL ASPECTS OF FŒTAL ERYTHROBLASTOSIS.[1]

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SINCE the work of Landsteiner and Wiener in 1940 in discovering the Rh factor, a great deal has been written on the subject of fœtal erythroblastosis. These contributions are widely scattered throughout the current literature. The obstetric staff of the Queen Victoria Hospital suggested therefore that a short paper on the ætiology and clinical aspects of the disease might be helpful.

Definition: Fœtal erythroblastosis is a familial disease manifesting itself in a triad of clinical entities, namely: (i) congenital œdema of the fœtus (fœtal hydrops), which is the most severe form. (ii) *icterus gravis*, and (iii) hæmolytic anæmia of the newborn, the last being the mildest manifestation. In addition, in these families a history is frequently given of repeated miscarriage, intrauterine fœtal deaths and premature still-births.

Nomenclature: The term fœtal erythroblastosis is misleading, as in a large number of cases there is no increase of erythroblasts in the peripheral blood. Also, erythroblasts in excess can occur in the blood in other conditions. It has been suggested that a better name would be "Rh incompatibility". In some cases, however, the incompatibility between mother and baby would appear to be concerned, not with the Rh factor, but with the A-B group-specific substances. It would seem, therefore, that "familial blood factor incompatibility" would be a better term.

Rh Factor: Landsteiner and Wiener, in the course of their experimental work, injected red blood cells from Rhesus monkeys into rabbits. They produced in the rabbits an anti-Rhesus serum, which agglutinated the monkey's red blood cells. This is known as the Rhesus antibody or the anti-Rh substance. It was then found that the anti-Rh substance caused agglutination of 85% of the red blood cells of white people, who were therefore termed Rh-positive, and that it failed to agglutinate the red blood cells of 15% of the white race, who were therefore termed Rh-negative.

The work of Simmons *et alii*[1] shows that some Asiatic races and Australian aborigines are uniformly Rh-positive.

According to Wiener, the Rh factor lies just below the surface of the red blood cell. Originally it was said that the Rh factor was present only in the red blood cell, but K. E. Boorman and B. E. Dodd,[2] using saline suspensions of ground-up tissues, in contrast to watery extracts previously employed, showed that it was present in the tissues, in some cases being present in higher concentration in the tissue cells than in the red blood cells. It was said to be almost entirely absent from the body fluids, but recently, Witebsky and Mohn[3] have found the Rh substance to be present in the amniotic fluid of four out of five Rh-positive fœtuses of Rh-negative mothers.

THE INHERITANCE OF THE RH FACTOR.

The Rh factor is carried by two allelic genes, the Rh-positive character being designated Rh, and the Rh-negative character being designated rh. One gene is inherited from each parent, and the Rh-positive gene acts as a Mendelian dominant. Therefore the individual possessing one Rh-positive gene is Rh-positive, as well as the individual who possesses two Rh-positive genes. The individual with two Rh-positive genes, (Rh Rh), is described as a homozygous Rh-positive subject. The individual with one positive and one negative gene (Rh rh) is described as a heterozygous Rh-positive subject. To determine whether the individual is homozygous or heterozygous, it is necessary to determine the Rh type of blood of both parents and siblings of the individual.

The individual with two Rh-negative genes (rh rh) is Rh-negative.

Rh Rh = homozygous Rh-positive = 37%, white race } 85% Rh-positive
Rh rh = heterozygous Rh-positive }
rh rh = Rh-negative; white race, 15% Rh-negative

It has been estimated that in ordinary mating, 13% of all marriages will occur between an Rh-negative woman and an Rh-positive man.

It has also been estimated that in 9% of all pregnancies an Rh-negative mother will carry an Rh-positive fœtus. More recent authorities give figures of 10·3% and 7·3% respectively.[4]

The following are the possible matings of an Rh-negative mother.

1. With a homozygous Rh-positive father the following may occur:

Mother: Rh-negative rh rh — Father: homozygous Rh-positive Rh Rh
= Rh rh, Rh rh

That is, all the children must carry one Rh-positive gene, and therefore all will be Rh-positive.

[1] Read at a meeting of the Queen Victoria Hospital Obstetric Staff, Melbourne, on July 25, 1945, and repeated at a meeting of the Melbourne Pædiatric Society on September 12, 1945.

2. With a heterozygous Rh-positive father the following may occur:

Mother: Rh-negative rh rh — Father: heterozygous Rh-positive Rh rh

= Rh rh, rh rh

The possible children are Rh rh (Rh-positive) or rh rh (Rh-negative). That is, there is a 50% chance of the couple having Rh-negative children.

3. With a Rh-negative father the following will occur:

Mother: Rh-negative rh rh — Father: Rh-negative rh rh

= rh rh, rh rh

All the children must be Rh-negative.

The Rh factor has been found not to be a simple entity, but to contain several subgroups, namely, Rh_0, Rh′, Rh″, Rh_1 (Rh_0 Rh′), Rh_2 (Rh_0 Rh″). With regard to the Rh factor, eight standard blood types are described:

Rh_0	2·5%	Rh-positive
Rh′	1·2%	
Rh″	0·3%	
Rh_1	54·5%	
Rh_2	15%	
Rh_1 Rh_2	13%	
Rh′ Rh″	1 in 10,000	
Rh-negative	13·5%	

These figures are given by Wiener for New York.

More recently an Hr factor has been described. The Rh′ people and some individuals of subgroup Rh_1 are said to be Hr-negative. All other Rh-positive subgroups and Rh-negative subjects are Hr-positive.

In contradistinction to the α and β agglutinins (anti-A in group B, anti-B in group A, respectively) which are normally present in the appropriate human serum, the anti-Rh substance never occurs naturally. It may be called forth in two sets of circumstances, namely: (i) by transfusion of Rh-positive blood into an Rh-negative man or woman, and (ii) in an Rh-negative woman pregnant with an Rh-positive fœtus.

The production of the antibody occurs in only a small proportion of such conditions. It is generally estimated to occur in about 2% to 4% of such cases, with regard to both transfusions and pregnancies. This works out to about 1 in 300 cases among all patients receiving blood transfusions, and 1 in 300 of all pregnancies. This last figure cannot perhaps be taken as authoritative, as mild cases of *erythroblastosis fœtalis* are not by any means always recognized.

An excellent article by Edith L. Potter on the present status of the Rh factor appears in the *American Journal of Diseases of Children*, Volume LXVIII, July, 1944, page 32.

The Anti-Rh Substance in the Pregnancy of an Rh-Negative Mother with an Rh-Positive Fœtus.

Mode of Production.

Some Rh-positive red blood cells from the fœtus escape through the placental circulation into the mother's blood stream. In 2% to 4% of cases—namely those in which the babies develop *erythroblastosis fœtalis*—the mother responds by producing the anti-Rh antibodies. It has been stated by Levine[6] on the basis of animal experiments, that the escape of one-fifteenth of a millilitre of red blood cell sediment from the fœtus per day into a woman weighing eight and a half stone for fourteen days would be sufficient to produce antibodies. Whether or not the mother produces antibodies depends probably on three factors: (i) the capacity of the mother to produce antibodies; (ii) the antigenic potency of the fœtal cells; (iii) possibly, also, the placental permeability.

The time of appearance of the antibodies—as demonstrated by *in vitro* methods—varies a good deal. They have been demonstrated as early as the twelfth week of pregnancy, but in many cases they are not apparent right up to the time of delivery. According to Boorman *et alii*,[7] the time when they are most easily demonstrated is from one to three weeks after birth.

It has been suggested that the reason for the late appearance of the antibodies is that during pregnancy they are absorbed by the fœtal red blood cells and tissues, and after birth they are free in the circulation. Others suppose that the antibodies are held by the reticulo-endothelial system and liberated after birth.

The time of disappearance of the antibodies also varies. They usually persist for some months, but in some cases they may persist for years, in one case for as long as eight years. While they persist, the mother may carry an Rh-negative fœtus without trouble, but an Rh-positive fœtus will probably be affected.

The titre of antibodies in the serum is usually not high, the usual figures being 1:4 to 1:8. Potter describes a case in which the titre was 1:5,000, and R. Jakobowicz found a titre of 1:4,000 in one of our cases. The severity of the effect on the fœtus is not found to run parallel with the titre of the mother's serum.

It is to be recalled that the demonstration of these antibodies *in vitro* is different from the reactions which take place in the fœtal body. Firstly, the red cells against which a suspected maternal serum is tested are frequently adult erythrocytes. It has been demonstrated that fœtal red blood cells differ from adult red blood cells, for instance, in such an important point as type of hæmoglobin. It has been shown that serum which fails to agglutinate adult cells will cause agglutination in cord blood.[8] Secondly, the medium in which the reaction takes place is different, in that fœtal serum is different from adult serum, or from the ordinary saline red blood cell suspension used in the laboratory. Thirdly, the agglutination shows whether any agglutinating effect is produced on the red blood cells; but it tells nothing of the effect produced on the cells of other organs.

The anti-Rh substance has been demonstrated in mother's milk, and in any case tests for it should be made. It can be destroyed by boiling the milk for three minutes. It has been questioned whether the antibodies can be absorbed from the alimentary tract; but clinical evidence would support the view that such absorption does take place.

Types of Antibodies Produced.

It would appear that several types of antibody may be produced: (i) agglutinins, (ii) hæmolysins, (iii) blocking antibodies, (iv) precipitin and (v) cytotoxins.[9] It had been noted frequently that in some cases of *erythroblastosis fœtalis* no antibodies could be demonstrated; yet clinically an Rh incompatibility apparently existed. Wiener has shown in such cases the presence of the blocking antibodies.

In the ordinary test for the anti-Rh agglutinin, the serum from the mother is put up with known Rh-positive cells. If the anti-Rh agglutinin is present, agglutination will occur. If, however, the mother's serum contains blocking antibodies, they have a higher affinity for the red cell than the agglutinins. They combine with the red cell and thus prevent the agglutinin from acting on the red cells. No agglutination therefore takes place. These blocking antibodies can be easily tested for and removed.

If the mother's serum prevents agglutination from taking place between known Rh-positive cells and known anti-Rh serum, it must contain blocking antibodies. These can be removed by absorption with Rh-positive cells of the appropriate subtype.

Effects of Anti-Rh Substances on the Fœtus in Utero.

In utero the fœtal red blood cells are destroyed to a varying extent by anti-Rh substances with the production of fœtal anoxæmia, which will have general systemic effects, and in particular greatly stimulate erythropoiesis. Immature red cells may therefore be present in the peripheral circulation in numbers greatly exceeding normal. It is possible also that there may be direct reactions between the cells of other tissues and the anti-Rh substances. The effect on the fœtus of the anti-Rh substances may be severe enough to kill it early in pregnancy, so that the mother miscarries, or it may be milder, so that she carries the infant to term.

Occasionally one encounters a case in which the mother's blood contains anti-Rh substance, but the fœtus is apparently unaffected. It is of course, possible that in these cases a late anæmia may occur. I have one such infant under treatment at present. This condition will be missed unless specifically looked for. These babies will also need to be followed for some time before we can exclude the possibility of latent systemic damage.

It is obvious that in erythroblastotic families the risk is greater to the life of each successive Rh-positive fœtus which the mother carries, as each such pregnancy stimulates antibody formation, and that rapidly recurring pregnancies increase that risk.

Anti-Hr Substance.

If an Hr-negative mother becomes pregnant with an Hr-positive fœtus, she may react by producing anti-Hr substances in the same way as has been outlined above for the Rh incompatibilities. In these cases both mother and child are Rh-positive.

Erythroblastosis Fœtalis.

It has been shown by Levine that 90% of cases of *erythroblastosis fœtalis* can be explained on the basis of Rh incompatibility. That leaves 10% to be explained on some other basis.

1. It has been demonstrated that some cases are due to incompatibility between the Rh subgroups. In these cases both the mother and fœtus are Rh-positive, but belong to different subgroups.

2. Some, as previously stated, may be due to Hr incompatibility. Here, again, both the mother and fœtus are Rh-positive.

3. In some cases the father and baby are Rh-negative, the mother is Rh-positive and no ABO incompatibility exists. These cases are ill understood at present, unless we regard the Rh-negative condition as an existing entity rather than as an absence of Rh.

4. Some cases are certainly due to ABO incompatibility, and I have now seen several such instances at the hospital.

If the mother belongs to blood group A, her serum contains the β agglutinin, that is, it contains the anti-B substance. Should she belong to blood group B, her serum contains the α agglutinin; that is, it contains the anti-A substance. Should she belong to blood group O, her serum contains the α and β agglutinins; that is, it contains both anti-A and anti-B agglutinins.

The average anti-A anti-B titre varies according to the technique used; with the technique described by Bryce and Jakobowicz[10] it is commonly about 1:64. A recent method in the United States of America gives much higher titres for α and β.

If the mother becomes pregnant with a fœtus of a blood group which she lacks (so-called heterospecific pregnancy), she may become immunized against her fœtus. She will then respond by an abnormally high rise in titre of the appropriate antibody. This may occur in an A group mother with a B or AB group fœtus; in a B group mother with an A or AB group fœtus; and in an O group mother with an A, a B or an AB fœtus. By following the titre of the mother's serum during pregnancy one can ascertain if this is taking place. According to Polayes,[11] there is usually a rise in normal heterospecific pregnancies to about 1:250. Should the titre rise to above 1:700, the fœtus may be affected. Titres of 1:2,000 and 1:4,000 are not uncommon, and the titre may rise as high as 1:16,000; this occurred in one of my cases, resulting in the premature birth of an infant with *erythroblastosis fœtalis*, who died of kernicterus on the second day.

Secretors and Non-Secretors.

Eighty *per centum* of the population have the agglutinogens (group-specific substance) A and B present in a water-soluble form in the body fluids, and are called secretors. In the remaining 20% it is not present in water-soluble form in the body fluids, and these subjects are termed non-secretors. Whether or not a person is a secretor is easily determined by testing the saliva. It has been said that it is safer for the fœtus to be a secretor, because the agglutinogen in the body fluids can neutralize antibodies if these are present and so protect the cells. More recently a different view has been advanced.[12] It is suggested that a secretor fœtus acts better as an immunizing agent than a non-secretor, and is therefore more likely to cause the production of antibody in the mother. In the heterospecific pregnancies associated with an abnormally high serum titre, in our series at the Queen Victoria Hospital, it has been found that the majority of the fœtuses were secretors.

Congenital Œdema of the Fœtus: Fœtal Hydrops.

Fœtal hydrops is the most severe manifestation of *erythroblastosis fœtalis*. The mother usually has hydramnios, and Gilmour[13] in his excellent article on the morbid anatomy of *erythroblastosis fœtalis*, found the average length of gestation to be thirty-three weeks. In his series the ratio of females to males was 2·5 to 1.

In these cases the liquor is bile-stained, greenish or yellow. The placenta is large, heavy and œdematous, and weighs about half the weight of the infant, instead of the usual one-seventh.

The infant may be still-born and is often macerated. If it is born alive, it usually survives for a matter of hours. One case has been reported in the literature in which the child was delivered by Cæsarean section, blood examination being immediately carried out and an exsanguination transfusion performed. The child survived; but in view of the widespread pathological changes which occur in this type of case, and the possibility that the child may survive with a damaged central nervous system, the advisability of the procedure is open to some doubt. Those infants born alive are œdematous. They frequently show petechiæ or ecchymoses, and may have blood-stained material oozing from the nose and mouth. The spleen is grossly enlarged, the liver being enlarged to a less spectacular degree. In the blood a gross degree of anæmia is apparent with large numbers of nucleated red cells of all types.

A distinction should be made here between the condition of *erythroblastosis fœtalis*, in which the erythroblastosis is secondary to blood destruction, and the condition of primary erythroblastæmia, in which nucleated cells are present in large numbers in the newborn owing to a fault in blood production. In *erythroblastosis fœtalis* the type of blood formation is normal for the age of the fœtus. In primary erythroblastæmia, in which the fault is fundamentally one of blood production, a type of blood formation persists, normal for a fœtus of an earlier age, but abnormal for the real age of the fœtus.

Macklin[14] has drawn attention to the fact that these two conditions can be easily distinguished by the fact that in *erythroblastosis fœtalis*, hæmosiderosis is invariably present in liver and spleen, and is shown by staining with Prussian blue. In primary erythroblastæmia hæmosiderosis is absent.

The post-mortem findings in congenital œdema of the fœtus are as follows:

1. The most striking feature is the abnormally active and widespread erythropoiesis, which is of normal type. This occurs in all the usual sites—for example, liver, spleen and bone marrow—and also in abnormal sites—for example, suprarenal, kidney, lungs, thymus, lymph glands, placenta.

2. Hæmosiderosis is present to a pronounced degree in liver and spleen, to a less extent in other organs.

3. Changes can also be demonstrated in practically every organ of the body.

Gilmour lays stress on the bright yellow colour of the inner layer of the suprarenal cortex, due to lipoid infiltration. He gives this as a characteristic post-mortem finding, and it has been obvious macroscopically in our cases. The liver he found to be enlarged in proportion to the increased weight of the œdematous fœtus.

The reticulin is increased in amount, in some cases producing a pronounced fibrosis. Some writers have called this fœtal cirrhosis and labelled it as a fourth type of *erythroblastosis fœtalis*.

In the liver cells spoiling is apparent, and a feature commented on by all observers is the presence of bile thrombi in the intercellular canaliculi.

The spleen is grossly enlarged out of proportion to the increased body weight of the infant, and as has previously been stated, is affected by pronounced erythropoiesis and hæmosiderosis.

The brain is usually damaged, particularly in the basal ganglia and to a less extent in the cortex. In one brain examined, the basal ganglia were so spoiled as to be practically invisible to the naked eye. It is to be noted that these changes occurred in the absence of jaundice.

In the pancreas there is an increase in the number and the size of the islets, and some authors have commented on the similarity of pathological changes, not only in the pancreas, but also in other organs, between fœtuses affected by *erythroblastosis fœtalis* and fœtuses of diabetic mothers.

The thymus is smaller than normal and all the glands tend to be hypoplastic.

In the bones a disturbance of endochondral ossification is apparent, with deficient activity of both osteoblasts and osteoclasts. This produces an increase in the number of trabeculæ of calcified cartilage and macroscopically gives an appearance resembling a deepened layer of provisional cartilage.

Alice Wheildon has drawn attention to the fact that the liver and spleen, being of large size, push up the diaphragm and encroach on the capacity of the thorax. As a result, the lungs are small and ill-expanded. She has noted in all our cases that the lungs were extensively mottled with extravasations of blood.

The placenta, as has previously been mentioned, is larger and heavier than normal. Microscopically[13] it looks younger than the fœtal age. The active villi larger than normal, the well-developed epithelium, the active stroma cells and the capillaries lined by cells with active nuclei, are all an effort to combat fœtal anoxæmia. Erythropoiesis is seen in the placenta.

It is obvious, therefore, that in congenital œdema of the fœtus there are, besides an active destruction of red blood cells and very active compensatory erythropoiesis, pathological changes in practically all the organs of the body, some of them, as in the brain, being irreversible. Possible causes of these pathological changes are as follows: (i) Long-standing anoxæmia in growing tissues. (ii) Direct action of the anti-Rh substance on Rh-containing cells. It is possible that the degree of Rh sensitivity of the cells of any particular organ may determine the extent of damage, different organs, therefore, suffering to different degrees in different fœtuses. In some the blood may bear the brunt of the attack, in others the liver, in others the central nervous system and so on: thus the foundation for the development of familial systemic disorders may be laid. (iii) Impaired function of one organ, for example, the liver, producing changes in other organs, for example, the brain. The giving of blood will only correct an existing anæmia. It cannot undo established pathological changes.

Icterus Gravis.

Formerly *icterus gravis* was said to be present if the jaundice came on within the first forty-eight hours, was severe, and was accompanied by anæmia. Since the recent work on blood-group incompatibility as the cause of the condition, we have found that these criteria do not apply. What, then, are we to take as standard indications of the disease? It is suggested that standard indications should be the occurrence of jaundice in the first week accompanied by the following abnormalities.

1. The presence in the child's blood of a blood factor which the mother lacks.

2. Demonstration of antibody for the baby's cells in the mother's serum. This cannot always be demonstrated, although recently the use of the test for blocking antibodies,[16] as well as the test for agglutinins, has greatly increased the percentage of instances in which antibodies are found. If antibodies cannot be demonstrated, it is suggested by Wiener *et alii*[17] that a biological test should be performed. In this the mother is given an intravenous injection of 50 millilitres of the father's blood. A positive biological result is the development of a chill by the mother and an increase in the bilirubin content of the serum. In some cases, however, untoward symptoms have occurred, and such a test is hardly likely to be popular.

3. Enlargement of the spleen. While in a certain proportion of normal newborn infants the spleen is palpable, in *icterus gravis* the enlarged spleen is a helpful positive finding. Potter in her article maintains that a spleen extending two centimetres or more below the costal margin (and weighing at post-mortem examination 25 grammes or more) is, in the absence of syphilis, pathognomonic of *icterus gravis*.

4. An immediate direct positive reaction to the Van den Bergh test. Academically this is helpful, but practically it is rather difficult to obtain the amount of blood necessary for the test unless a vein is cut down upon. Puncturing of the fontanelle for blood in jaundiced infants is a dangerous procedure, owing to the hæmorrhagic tendency which may be present.

5. The presence of bile in the urine.

6. A family history of other manifestations of *erythroblastosis fœtalis*.

7. The subsequent clinical history and pathological findings.

Pathological Findings.

The pathological findings are essentially similar to those in congenital œdema of the fœtus, but milder in degree. In *icterus gravis*, no lipoid staining of the cortex of the suprarenal is evident. Gilmour draws attention to the characteristic bile staining of the pyramids of the kidneys.

All observers stress the typical three findings in the liver—namely, hæmatopoiesis, hæmosiderosis, and the presence of bile thrombi in the intercellular canaliculi. The liver cells are degenerated, in some areas the cells have necrosed and disappeared. In some cases at post-mortem examination evidence of liver-cell regeneration was present. In some instances the lungs showed the small size and hæmorrhagic areas, previously described by Alice Wheildon in congenital œdema of the fœtus.

The state of the brain is of interest in connexion with the sequel of kernicterus. In this condition the basal ganglia are the most severely affected portions of the brain, standing out bright yellow as though coloured with yellow paint. The colour is, of course, due to the deposition of bile. Degeneration and necrosis of the ganglion cells are described, and in some cases areas of necrosis occur in the white matter. In older infants demyelinization of the axones and increase in neuroglial tissue may be found. The relationship between disease of the liver and the basal ganglia has been commented upon by various writers. It has been pointed out that those poisons which affect the liver also affect the basal ganglia. In Kinnier Wilson's syndrome there is again the association of hepatic disease and lenticular degeneration. It is possible that such cases have their origin in *icterus gravis*.

Symptoms.

The outstanding symptom is jaundice, the time of onset of which varies. In severe cases it may be obvious within two hours of birth and is generally present within forty-eight hours. In mild cases it may not come on till the third or fourth day. It is of interest to note that the infant is not jaundiced at birth. The reason advanced by Dr. H. Bettinger, of Melbourne, and by other observers, is that during the fœtus's intrauterine life the mother excretes the bile for the fœtus. The degree of icterus varies considerably. In some cases it is intense, the baby being a bright golden yellow. In less severe cases the degree of jaundice is correspondingly less pronounced.

The duration of the jaundice is variable. In mild cases it may last about one week. In other cases it may last as long as two or three months.

In the severest cases the baby is desperately ill. The intense jaundice produces yellow sclerotics and heavily bile-stained urine. Fever, some degree of œdema and ecchymosis may be present. Head retraction frequently occurs with rigidity of the limbs. The babies die within the first two or three days, sometimes with cerebral symptoms of twitchings and convulsions. At other times respiratory

symptoms are more obvious, with dyspnœa, cyanosis and moist adventitiæ in the lungs.

In these fulminating cases the outlook in spite of treatment is almost universally bad.

In the milder cases the infant may show drowsiness, some pyrexia and slight œdema. The appetite may be poor, and vomiting and digestive difficulty may occur. The stools may contain ill-digested material and be green and curdy. They are usually of normal colour, but in some cases there may be biliary obstruction, and for a time the stools may be practically colourless, so that the condition simulates congenital obstruction of the bile ducts. The spleen is enlarged, the liver to a less extent. The urine is bile-stained.

A hæmorrhagic tendency may be present. This may be due (*a*) to a diminished coagulability depending on the low blood prothrombin content or diminished fibrinogen secondary to the hepatic spoiling, or (*b*) to anoxæmia. Probably both factors are responsible. Petechial hæmorrhages may be present in the skin. Hæmorrhage may occur from the usual sites. Occasionally it may occur from the pharynx and prove fatal, owing to aspiration of blood.

In the past it has been assumed that in all cases of *icterus gravis* anæmia was present, but this is not so. In some infants anæmia is present at birth, the hæmoglobin value not infrequently being 45% (as against the normal figure for newborn babies of 130% to 140%, 13·8 grammes of hæmoglobin per 100 millilitres being taken as a standard), and the red cell count being 2,000,000 or so (as against the normal newborn count of six or seven million). Lower erythrocyte counts and hæmoglobin values than these also occur. In other infants the red cell count is normal at first, but drops rapidly within the next few days thereafter, often falling by 1,000,000 cells per cubic millimetre per day. Other infants may have a normal red cell count till after the jaundice has disappeared, and may then, at the age of two or three weeks, develop progressive anæmia.

In still other babies, even though pronounced jaundice has been present and antibodies have been demonstrated in the mother's blood, no anæmia develops, even after several months. It is obvious, therefore, that in *icterus gravis* a dissociation of jaundice and anæmia can and does occur.

It is generally assumed that the jaundice is due to blood destruction; but those cases in which jaundice occurs without anæmia would indicate that this is not so. One assumes that in these cases the brunt of the attack by the antibodies has fallen on the liver and not on the blood. The spoiled liver is unable to deal with the ordinary amount of bilirubin brought to it, and so jaundice occurs. One can suggest as an hypothesis that in these cases the Rh sensitivity of the liver cells is higher than the Rh sensitivity of the red blood cells, and so the liver is more severely affected.

The films may show an excess of nucleated red cells or may be normal, thus demonstrating the unsuitability of the term "fœtal erythroblastosis".

In any case of *icterus gravis* in which anæmia is present, blood examinations should be made each day. In those cases in which no anæmia is present the examination should be made three times a week, then twice a week, and later once a week till the end of six weeks. After that time, the blood count is not likely to drop. The jaundice masks the anæmia clinically, and unless blood examinations are made, the real extent of the anæmia may not be appreciated.

The terms "kernicterus", "nuclear jaundice" or "cerebral jaundice" are used rather loosely to describe both cases in which the baby shows evidence of involvement of the central nervous system from birth, and also cases in which the cerebral damage becomes obvious as a sequel, weeks or months after the subsidence of the jaundice. In those cases in which the symptoms are present from the early days of life, the jaundice usually persists for a longer time than normal—namely, six to eight weeks. There is no association between the degree of anæmia and the development of kernicterus. The babies show head retraction, opisthotonus and frequently rigidity. They may present a wild expression, restlessness or apathy, and are often difficult to feed. Sweating is sometimes a marked feature. They usually gain in weight slowly.

Sequelæ.

Late anæmia may come on, as has previously been stated, up to five or six weeks after birth, and some weeks after the jaundice has disappeared. It is generally assumed that the anæmia is hæmolytic, but it is difficult to understand why the hæmolysis should occur so long after birth. It would appear more likely to be due to faulty production of red blood cells than to destruction of existing cells. There is some pathological evidence to support the view that there is a hold-up in erythropoiesis, and it is well known that these babies may have for some weeks only the donor's cells in the blood stream. In one of our babies, an Rh-positive infant requiring nine transfusions, for some weeks only Rh-negative cells from his blood transfusions were demonstrable in his blood. This occurred after the original jaundice had subsided. This failure to produce blood normally may be due to a late effect of liver damage—for example, to failure to store the anti-anæmic factor, or to a direct toxic effect on the erythropoietic tissue.

Previously it was held that kernicterus was due to the toxic effect of the bile on the brain; but all the evidence is against this view. In cases of congenital biliary obstruction, in which the infant survives for many months, frequently into the second year, with gross jaundice, kernicterus does not occur. Why, then, should it occur in conditions such as *icterus gravis*, in which the jaundice lasts only for a matter of weeks? Further, cerebral damage has been demonstrated in the brain of infants who have died of congenital œdema and who have never been jaundiced, and in these babies the pathological changes are similar to those associated with kernicterus. It is more probable that the intense yellow colouring of the basal ganglia and to a less extent of the cerebral cortex is due to a deposition of bile in previously damaged tissue—what has been described as intravital staining. The possible causes of the damage to the nervous tissue have been suggested earlier.

The symptoms noted are mental defect, epilepsy (both major and minor), spasticity, ataxia, nystagmus, and choreiform and athetoid movements. These infants frequently have poor vitality and may die in the first year from intercurrent infections.

We know that these changes can occur after *icterus gravis* with prolonged jaundice, but it is interesting to speculate as to whether the brain changes can occur when jaundice is slight or absent. In the opinion of Yannet and Lieberman[13] this is so. In an institution for mentally defective children they found a much higher incidence of Rh incompatibility in mother and child than in the ordinary population. They also reported having found in a further series of 200 mentally defective children a higher incidence of incompatibility in the ABO group than among normal children. This opens up an interesting field from the ætiological standpoint, in the elucidation of familial as opposed to hereditary diseases. For example, we had at the hospital recently a mother who had borne six children. Of these, three were healthy and survived, while the remaining three died of Werdnig-Hoffman's disease. The mother was of blood group B. The father was of blood group A. Of the three surviving children, two were of blood group B, and the third was of blood group O. Thus the blood of all these three survivors was compatible with that of the mother. We were able to determine the blood group of one of the babies who died of Werdnig-Hoffman's disease; the baby belonged to blood group A and was a non-secretor. It is possible that the incompatibility between mother and fœtus may have accounted for the condition. It can be suggested that the fœtal motor nerve cells were particularly sensitive to the mother's anti-A substance, and as the fœtus was a non-secretor, there were no group A agglutinogens in the tissue fluids to protect the nerve cells. In such a case

the titre of the mother's anti-A agglutinin would not be unduly raised, as there was no evidence of an effect on the infant's blood. In this instance the titre was 1:32. One would probably have to test the maternal serum against tissue cultures of motor nerve cells—a more formidable proposition than the ordinary agglutination test.

Bile-stained teeth were first described by Ellis in 1938. I have seen elsewhere one such case, in which the substance of all the milk teeth was noticeably green.

Albright's syndrome (polyostotic fibrous dysplasia or *osteitis fibrosa disseminata*) was first described by Braid[29] in 1932. In this condition, progressive fibrocystic disease of the bone appears first on one side of the body and becomes bilateral, being associated with much deformity. Cutaneous pigmentation occurs, and in female children sexual precocity, so that the infants may menstruate at the age of two years.

Hepatic dyspepsia is commonly met with in these infants and children.

Hepatic cirrhosis is described as a sequel to *icterus gravis*.

As has previously been suggested, Kinnear Wilson's syndrome is probably a sequel to infantile *icterus gravis*.

Differential Diagnosis.

Physiological icterus is a somewhat indefinite clinical entity, and the jaundice appears on the third or fourth day; but, as has previously been stated, the age of incidence of the icterus cannot be taken as a standard, nor can the fact that the jaundice generally clears by the tenth day. The jaundice is usually moderate in degree. The Van den Bergh test produces an indirect reaction, and bile is generally absent from the urine. The spleen is normal in size. No untoward symptoms are present, save some drowsiness and disinclination to feed. The blood groups of mother and baby are compatible, or if they are incompatible, no antibodies are demonstrable in the mother's serum if looked for from the seventh day on. The subsequent history of the baby is normal in the neonatal period, and there is no family history of fœtal erythroblastosis.

Septic jaundice can be distinguished by the associated symptoms.

Jaundice complicating infections—for example, bronchopneumonia—can also be differentiated by the obvious presence of the causative condition.

Congenital syphilis may present with jaundice, but the associated syphilitic manifestations and the Wassermann test differentiate this type of icterus.

Congenital obstruction of the bile ducts, which produces completely colourless stools, may be confused with *icterus gravis*, in which for a time the stools may be colourless. In congenital biliary obstruction, once the meconium has been passed, the stools become colourless and remain so, whereas in *icterus gravis* the stools are usually normal at first, only later becoming temporarily colourless. After a period of some days to a week of white stools, the colour usually returns to the fæces. Also in *icterus gravis* the jaundice always appears in the first week, whereas in biliary stenosis it is not present before the end of the first week and is sometimes later in onset. The enlargement of the spleen, the blood changes if present, and the positive serological findings in *icterus gravis* also assist the diagnosis.

Acholuric family jaundice in the newborn is occasionally encountered. It can be distinguished by the presence of a family history and of microspherocytosis. The fragility test is also employed in differentiating the condition. Leonard Findlay[30] states that in newborn infants the fragility is slightly less than in adult life. The serological findings characteristic of fœtal erythroblastosis are absent.

Prognosis.

In the fulminating form the outlook is bad; the infants generally die. Some authorities have advocated heroic treatment in the form of exsanguinating transfusions; but when one considers the almost certain association of central nervous system damage and kernicterus, the advisability of such a procedure is open to question.

In the ordinary case the immediate prognosis is good. When the remote prognosis is considered the possibility of sequelæ must be borne in mind. The incidence of kernicterus is difficult to assess, since there is no doubt that many cases of the milder type of *icterus gravis* are overlooked. Most estimates of the incidence of kernicterus, therefore, are likely to be too high. Diamond assesses it as 15%.[31]

The follow-up, over a period of years, of infants who have suffered from *icterus gravis* will be interesting, and may yield information helpful in elucidating the ætiology of conditions hitherto unexplained.

Treatment.

Treatment is directed mainly along these lines: (i) measures to correct the anæmia; (ii) treatment to assist the damaged liver; (iii) supportive treatment.

In any case in which anæmia is present, blood examinations should be made each day and transfusions given as required. The critical level is generally taken as 3,000,000 red blood cells per millilitre and a hæmoglobin value of 60%. If the blood picture falls below this level, a transfusion is necessary.

The donor's blood must be compatible with the infant's blood and the blood must be Rh-negative. Although the baby himself is Rh-positive, he contains in his blood anti-Rh substance from the mother, which will agglutinate the cells of an Rh-positive donor. It is stated by some authorities that in an emergency Rh-positive donors can be used. This is a dangerous procedure, and I should think that Rh-positive donors should never be used.

In a case encountered elsewhere, the infant was given a transfusion of Rh-positive blood. The red cell count dropped from 3,000,000 to 800,000 per cubic millimetre in forty-eight hours. The baby nearly died, requiring eighteen ounces of Rh-negative blood before it was out of danger. It was obvious that, not only had the donor's red cells been destroyed, but the transfusion of adult Rh-positive cells had stimulated the destruction of the infant's own red cells.

If an Rh-negative donor is unprocurable, Wiener[32] suggests that the mother's red blood cells washed free of antibody can be used. The mother's citrated blood is washed twice with saline solution, thus being freed of the plasma. The washed cells are then suspended in compatible plasma. Mollison[33] showed that whereas Rh-negative cells remained in the infant's circulation for as long as three months, Rh-positive cells were often destroyed within four or five days.

In choosing a donor, Wiener suggests testing the donor's cells against the mother's serum as an additional safeguard.

The number of blood transfusions needed will vary. Some infants require none. Others may require three or four, and as previously stated, one infant in our series required nine transfusions.

The Amount of Blood to be Transfused.

The amount of blood required to raise the baby's hæmoglobin value to 100% is usually reckoned from the following formula:[34]

$$\frac{100 - \text{baby's hæmoglobin value}}{100} \times \text{baby's blood volume}$$

The blood volume of the infant is stated by Windle, in his "Fœtal Physiology", to be, at any rate for the first day of life, two and a third ounces of blood for each pound of the baby's body weight. De Marsh *et alii*[35] give the blood volume for the first three days as 1·888 ounces per pound of body weight. Probably a round figure of two ounces per pound of body weight is a reasonable clinical estimate. When the volume reaches the adult standard of one and a third ounces per pound of body weight is not clear.

The amount to be given at any one time is stated by most authorities as half an ounce of blood per pound of body weight. This appears to be a safe rule clinically. If larger amounts are given, there is a risk to the baby's circulatory efficiency, and even when smaller amounts

have been given, the infant has been known to develop symptoms of respiratory distress and die after receiving one or two ounces of blood. Wheildon's observations on the small thoracic capacity probably explain these cases. Our usual procedure is to give half an ounce of blood per pound of body weight and to keep a careful watch on the infant, the blood being given slowly. In most cases the blood is injected, as the veins are so small that a drip transfusion is impracticable. If the total amount of blood required exceeds the half-ounce per pound, the transfusion needle, with the trochar *in situ*, is left in the vein, and the remainder of the blood is given after an interval of two to four hours, when it is assumed that the circulation has adjusted itself to the increased blood volume. No untoward results—for example, embolism—have been experienced. To centrifuge the blood, or to allow the blood to settle and give the red blood cream, is often a useful measure. The giving of too large volumes of blood not only causes circulatory and respiratory embarrassment, but by raising the hæmoglobin value above 100% throws unnecessary work on the inefficient liver, and further increases the jaundice, to the baby's detriment.

Blood counts should be made as a routine measure till the infant is three months old.

The breast milk is tested for antibodies, and should they be present, the infant is artificially fed. Till they are tested for on the seventh or eighth day, the milk can be expressed, boiled for three minutes and then safely given to the baby. Theoretically this procedure could be continued till the antibodies disappeared from the milk; but since the time of this is uncertain and the process of expression and boiling is tedious, it is usually not persevered with. Whether it is safe to assume that because antibodies are not demonstrated in the milk the baby can go to the breast with impunity is open to some doubt. In one such case it appeared that putting the baby to the breast under such conditions caused a considerable exacerbation of the anæmia. Some authorities deny that antibodies can be absorbed from the alimentary tract.

Empirically we follow at present the procedure of boiling the milk to the seventh or tenth day and giving it to the baby. We then test the milk for antibodies. If these are present we feed the baby artificially, and if they are absent we let the baby go to the breast.

Measures are directed to assisting the damaged liver. The infants are given two millilitres of crude liver extract (for example, "Campolon") by intramuscular injection twice a week, in the expectation that this measure will supply some principles which may not be elaborated satisfactorily by the infant's own liver. This is continued in the ordinary case till the jaundice clears.

Since it is held that the vitamin *B* complex helps liver function, this is given by mouth. Half a capsule of "Combex" per day has been the dosage used.

The administration of vitamin *K* analogue is indicated, since the liver damage may cause deficient production of prothrombin. It is true that to present the liver with vitamin *K* is no guarantee that this substance will be converted into prothrombin; but one would expect that the larger amount of vitamin *K* available would help in the production of prothrombin, even by an inefficient liver.

Finally, the feeding must be watched. Not infrequently these babies are unable to manage the ordinary amounts of fat, even that in breast milk, and a preparation low in fat content—for example, Nestlé's sweetened condensed milk—may need to be employed temporarily, occasionally for some weeks.

Babies with severe *icterus gravis* are very ill, and will naturally receive the general care accorded to any sick infant. In cases associated with pronounced splenic and hepatic enlargement, or with a hæmorrhagic tendency, the routine continuous administration of oxygen is indicated, in the former type because of probable small thoracic capacity, and in the latter because of probable anoxæmia. This measure should be alternated with the administration of "Carbogen" for five minutes per hour and can with advantage be carried out for forty-eight hours or longer if this is deemed necessary.

Hæmolytic Anæmia of the Newborn.

In hæmolytic anæmia of the newborn, anæmia occurs without jaundice. The anæmia may be evident at birth or may be delayed for some weeks. It may be moderate or extreme in degree, the red cell count dropping to less than 1,000,000 per cubic millimetre. No other symptoms are observed, and the infant usually gains in weight satisfactorily. The spleen is enlarged. The tendency is for the anæmia to be of the macrocytic type. Several cases of ABO incompatibility fall into this type of hæmolytic anæmia.

Although these cases are called hæmolytic anæmia, it is possible that the anæmia is due to a disturbance of red blood cell formation, rather than to blood destruction. As has previously been stated, it is hard to understand why the anæmia should come on some weeks after birth, when one would expect the antibodies to be diminishing. The presence of a macrocytic type of anæmia also tends to point to some defect in erythropoiesis.

It is of interest to note that prior to knowledge of the Rh factor, when infants suffering from fœtal erythroblastosis were transfused with blood which was almost certainly Rh-positive, cases frequently occurred among *icterus gravis* infants in which the blood counts were lower after transfusion than before it. I cannot remember having seen this happen in a case of hæmolytic anæmia, and it would suggest that in these cases the anti-Rh substance had disappeared from the blood. This would indicate that the anæmia was not hæmolytic. Disturbance of blood formation, as has previously been suggested, may be due to interference with liver function and to failure to store the anti-anæmic factor, or to direct toxic effect on erythropoietic tissue. Whatever the cause, the disturbance of function is temporary only, and if the infant is kept alive with transfusions, the anæmia disappears. The prognosis is good.

Diagnosis.

The diagnosis from other anæmias is made on the family history, on the finding of incompatible blood groups in mother and child with the presence of either anti-Rh agglutinins or a high anti-A or anti-B titre in the mother's serum against the baby's red cells (provided this test is made within three to four weeks of birth), on the tendency to macrocytic anæmia, on the enlarged spleen and on the absence of blood findings such as occur in other conditions—for example, microspherocytosis in acholuric family jaundice.

Treatment.

Treatment consists in blood transfusion, as in *icterus gravis*, whenever the red cell count drops below 3,000,000 per cubic millimetre or the hæmoglobin value below 60%. As in *icterus gravis*, Rh-negative donors of a suitable blood group are chosen (because of the theoretical possibility of presence of anti-Rh agglutinins).

It is advisable also to give two-millilitre injections of crude liver extract twice a week intramuscularly. Care should be taken that these injections are given into the correct portion of the buttock if this site is used—namely, the upper and outer quadrant. It is desirable also that they be given with an autoclaved syringe.

Prevention of Erythroblastosis Fœtalis.

Up to the present time no successful prophylactic measure has been evolved against *erythroblastosis fœtalis*. It has been suggested that the mother might be immunized against the husband's red cells, but this is apparently not practicable.

Attempts have been made, by terminating the pregnancy prematurely by Cæsarean section, to remove the fœtus from its hostile uterine environment. The results have not been encouraging. The hazards of prematurity in these cases—and probably the anæmia associated with the premature state—counterbalance the advantage of early termination of the pregnancy.

Potter suggests that artificial insemination by an Rh-negative donor might be considered in these cases. One such case has been recorded, with the birth of an Rh-

negative infant; but this procedure is not likely to have a wide application.

It would appear, therefore, that the discovery of the Rh factor has elucidated the ætiology of this hitherto inexplicable disease, and enabled us to save babies who would otherwise die of anæmia or from incompatible blood transfusion. It has, however, not given us, up to the present, any means whereby the disease in erythroblastotic families can be prevented, nor can we prevent the damage done to fœtal organs *in utero*. It is possible also that the damage done to different organs by this disease may be the basis of some of the familial as opposed to hereditary disorders and abiotrophies of later life.

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REFERENCES.

(1) R. Simmons *et alii*: "The Rh Factor: Ethnological Aspects", THE MEDICAL JOURNAL OF AUSTRALIA, May 27, 1944, page 483; "The Rh Factor in the Blood of Australian Aborigines", THE MEDICAL JOURNAL OF AUSTRALIA, June 17, 1944, page 553.

(2) K. E. Boorman and B. E. Dodd: "Group-Specific Substances A,B,M,N and Rh: Their Occurrence in Tissues and Body Fluids", *The Journal of Pathology and Bacteriology*, Volume LV, July, 1943, page 329.

(3) E. Witebsky and J. F. Mohn: "Investigations on the Occurrence of Rh Substance in Amniotic Fluid", *The Journal of Experimental Medicine*, Volume LXXXII, August 1, 1945.

(4) J. B. Haldane: "Selection against Heterozygosis in Man", *Annals of Eugenics*, Volume II, 1943, page 333.

(5) A. J. McCall and L. S. Holdsworth: "Hæmolytic Disease in the Newborn Caused by Antibody St.", *Nature*, Volume CLV, 1945, page 788.

(6) P. Levine: "The Pathogenesis of Fœtal Erythroblastosis", *The Journal of Pediatrics*, Volume XXIII, 1943, page 656.

(7) K. E. Boorman, B. E. Dodd and P. L. Mollison: "Clinical Significance of the Rh Factor", *British Medical Journal*, Volume II, 1942, page 535.

(8) A. G. Foord: *The Journal of the American Medical Association*, Volume CXXVII, March 17, 1945, page 638.

(9) R. W. Koucky: "Experience with Rh Substance in Transfusion Reactions", *Minnesota Medical Journal*, Volume XXVI, 1943, page 980.

(10) L. Bryce and R. Jakobowicz: "The Estimation of the Iso-agglutinin Titre of Human Serum and its Practical Applications", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, 1941, page 290.

(11) S. H. Polhayes: "Fetal Erythroblastosis in Mothers with Rh Positive Blood", *American Journal of Diseases of Children*, Volume LXIX, February, 1945, page 99.

(12) G. H. Smith: "Iso-agglutination Titres in Heterospecific Pregnancies", *The Journal of Pathology and Bacteriology*, Volume LVII, January, 1945, page 113.

(13) J. R. Gilmour: "Erythroblastosis Fœtalis", *Archives of Disease in Childhood*, Volume XIX, March, 1944, page 1.

(14) M. Macklin: "Erythroblastosis Fœtalis: A Proposed Definition and Clarification of the Term", *American Journal of Diseases of Children*, Volume LXVII, June, 1944, page 445.

(15) L. M. Hellman and A. P. Hertig: "Pathological Changes in the Placenta Associated with Fetal Erythroblastosis", *The American Journal of Pathology*, Volume XIV, 1938, page 111.

(16) A. S. Wiener: "New Test (Blocking Test) for Rh Sensitization", *Proceedings of the Society of Experimental Biology and Medicine*, Volume LVI, 1944, page 173.

(17) A. S. Wiener, I. B. Wexler and E. Gowrin: "Hemolytic Disorders of the Fetus and Newborn with Special Reference to Transfusion Therapy and the Use of the Biologic Test for Detecting Rh Sensitivity", *American Journal of Diseases of Children*, Volume LXVIII, November, 1944, page 317; H. Bettinger: personal communication.

(18) H. Yannet and R. Lieberman: *American Journal of Diseases of Children*, Volume LXIX, May, 1945, page 326.

(19) F. Braid: "Osseous Dystrophy following Icterus Gravis Neo-Natorum", *Archives of Disease in Childhood*, Volume VII, 1932, page 313.

(20) L. Findlay: "The Fragility of the Red Cells to Hypotonic Saline in Infancy and Childhood", *Archives of Disease in Childhood*, Volume XX, June, 1945, page 64.

(21) L. Bryce: Personal communication.

(22) A. S. Wiener: "Rh Blood Types and Some of their Applications", *American Journal of Clinical Pathology*, Volume XV, March, 1945, page 106.

(23) P. L. Mollison: "Survival of Transfused Erythrocytes in Hæmolytic Disease of the Newborn", *Archives of Disease in Childhood*, Volume XVIII, 1943, page 161.

(24) H. L. Marriott and A. Kekwick: "Volume and Rate in Blood Transfusion for Relief of Anæmia", *British Medical Journal*, June 29, 1940, page 1043.

(25) Q. B. de Marsh, W. F. Windle and H. L. Alt: "Blood Volume of Newborn Infants in Relation to Early and Late Clamping of Umbilical Cord", *American Journal of Diseases of Children*, Volume LXIII, June, 1942, page 1123.

NON-GONOCOCCAL URETHRITIS IN AUSTRALIAN TROOPS STATIONED IN BORNEO.

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THE prevalence of non-gonococcal urethritis among Australian soldiers was reported in 1942 by Willis[1] and by Gibson,[2] who estimated that some 45% to 60% of cases of urethral discharge were caused by some agent other than *Neisseria gonorrhœæ*. Non-specific urethritis has become a well-recognized clinical entity in military hospitals, although there is still no clear evidence as to its ætiology. It is characterized by a long incubation period, a persistent early morning discharge and a failure to respond quickly to chemotherapy. The disease in Australia appears to have a wide distribution in every State. Johnston and McEwin[3] have reported two cases in which they were able to demonstrate intracellular inclusion bodies in urethral smears, and they suggested that the disease might be due to a virus, or to an organism of the pleuropneumonia-like type; Beveridge[4] and Beveridge, Campbell and Lind[5] have successfully cultivated pleuropneumonia-like organisms from the normal male urethra, from the *cervix uteri*, and in 20% of cases of non-specific urethritis in men, but have been unable to assign a definite ætiological role to these bacteria. Johnston and McEwin also cultivated similar organisms in their inclusion body cases.

In view of these reports it was decided to make a routine examination for inclusion bodies in all cases of non-gonococcal urethritis at a military hospital in North Queensland. Of the first 34 patients examined, in eight instances inclusion bodies were found in the one smear examined. Had a more intensive search been made, it is probable that a higher percentage of positive results would have been obtained. When it was later found that non-specific urethritis was occurring amongst troops stationed in the Netherlands East Indies, whose only contact was with the local Indonesian and Chinese population, it became of interest to see whether inclusion bodies could be demonstrated here also.

Investigation of Cases.

The only subjects available for investigation in this study were healthy Australian soldiers, who had contracted their infection in widely separated areas in Borneo, and had been evacuated to Morotai for non-medical reasons. Primary infections were not found to occur in the Morotai area. Thus it has not been possible to assess the incidence of the disease as a whole, or in relation to other venereal infections. Inquiries have revealed that cases of all the common types of venereal disease occurred among troops on Borneo, and that of these, non-specific urethritis was responsible for the bulk of hospital admissions.

The clinical features corresponded closely to those found in Australia. They were an incubation period of one to

four weeks, a thin purulent discharge, often present only in the mornings, which persisted for seven to twenty days, an absence of dysuria or other symptoms, and no noticeable response to sulphonamide or penicillin therapy. In all, nineteen patients were examined, and in ten instances typical inclusion bodies were present in smears. The main findings in these cases are set out in Table I.

All patients admitted having had recent contact with Indonesian, Chinese or half-caste girls of good appearance, and although prophylactic measures were available, they were not taken during intercourse. Owing to the frequency of intercourse it was difficult to determine the exact incubation period. In one instance (Case VI), in which there had been only one exposure, it was accurately given as twenty days, while in six others it could not have been less than ten days. In the nine cases in which inclusion bodies were not recognized, the histories were similar to the others. Seven patients when first examined had had a discharge for more than fourteen days, and insufficient exudate was obtained for suitable smears. In the two other cases the smears were so heavily contaminated with bacteria, chiefly diphtheroid bacilli, that satisfactory examinations could not be made. Thus, in this small series, inclusion bodies were found in all smears which might reasonably have been expected to show them.

All patients were given a course of treatment with sulphamerazine or penicillin, under which their urethritis slowly subsided. The majority were free from symptoms and returned to their units in two to four weeks after their admission to hospital.

Laboratory Findings.

Smears were obtained by introducing a platinum loop into the urethra and gently scraping cells and exudate from the mucous membrane. Leishman's stain was used for the inclusion bodies and Gram's stain for bacteria. Cultures were made on blood-agar and on 30% horse serum and agar, incubated for seven days at 37° C. It was not possible under army conditions to prepare the special "V.F." medium recommended by Beveridge[4] for the isolation of pleuropneumonia-like organisms.

As indicated in Table I, inclusion bodies were present in varying numbers. They stained a bluish-purple, showing up clearly in the pale blue cytoplasm of the cells. It was sometimes necessary to make prolonged examinations of several slides before finding typical "infected" cells, while in other smears they could be seen in almost every field. They corresponded with the description given by Johnston and McEwin,[3] whose slides I had had the opportunity of examining before this investigation was started. The bodies appeared as tiny, discrete, ovoid or rod-shaped particles arranged in small masses or clusters in the cytoplasm of large epithelial cells. They were never found in leucocytes or in the smaller epithelial cells, and intranuclear forms were not observed. On close inspection they were found to have a characteristic morphology, which differentiated them from the rickettsiæ seen in murine and scrub typhus and from the elementary bodies of the psittacosis and *lymphogranuloma inguinale* group of viruses. Owing to their small size (0·3μ to 0·5μ) careful focusing and critical illumination were necessary to observe the various shapes. The most striking form was a minute ring with a delicate sharp outline and one or more thickenings at the poles. Vibrios, rods and coccal forms were also seen, and in some smears these predominated, while in others chiefly the ring types were found. In every case, however, a thorough search revealed some cells containing the rings. Extracellular forms, identical with the intracellular bodies, were noticed, and in one case were particularly numerous, lying singly and in clumps in streaks of diced mucus. There was no indication as to whether these represented an extracellular multiplication or were merely liberated from the cell cytoplasm in the process of preparation of the smear.

Bacteria were occasionally found in the urethral smears, being usually Gram-positive cocci or bacilli. In four cases the inclusion bodies were the only visible forms of micro-organism to be seen.

Smears were taken on the patient's admission to hospital and thereafter every two or three days until he was discharged. Inclusion bodies were present in decreasing numbers during the first week and were usually absent in the second week, although pus cells and epithelium were still found.

Cultures made from the exudate grew only colonies of *Staphylococcus albus* and diphtheroid bacilli. No pleuropneumonia-like organisms were isolated, even though a special examination was made for microcolonies during the seven days' incubation.

Discussion.

The frequency with which non-gonococcal urethritis is seen in army hospitals provides a stimulus for the collection of data regarding its ætiology and epidemiology. Although the position is still far from satisfactory, certain definite facts and lines of work are emerging. That such cases did not attract great attention before the war is almost certainly due to the much better facilities for investigation provided by the military medical organization, whereby patients can be observed in hospital throughout the course of their infection. In civil life a patient reporting in the afternoon to a busy clinic might well present so few symptoms that treatment would not be considered necessary. Nevertheless, it is likely that many of the non-gonococcal cases seen in civil clinics are in fact of the "inclusion body" type. Information about the transmission of infection is incomplete, as no adequate survey of female contacts has yet been published. Beveridge, Campbell and Lind cultivated pleuropneumonia-

TABLE I.

Case Number.	Day of Disease on Patient's Admission to Hospital.	Contact.	Incubation Period. (Days.)	Previous History.	Inclusion Bodies.
I	12	Indonesian.	12–28	Nil.	++
II	6	Chinese.	3–24	Nil.	+++
III	7	Chinese.	7–21	Non-specific urethritis, 1943.	+
IV	14	Indonesian.	4–26	Nil.	++
V	7	Indonesian.	21–40	Nil.	±
VI	2	Indonesian.	20	Nil.	++
VII	4	Indonesian.	19–24	Nil.	+
VIII	2	Chinese.	15–29	Nil.	+
IX	1	Indonesian.	10–31	Gonorrhœa, 1944.	++
X	17	Chinese.	12–22	Nil.	+

like organisms from three out of eleven cervical swabs from women from whom men had contracted non-specific urethritis.

The disease is undoubtedly widespread in Australia, and it seems reasonable to conclude from the random selection of this small group of cases that it has a wide distribution in Borneo and possibly throughout the East Indies.

The nature of the inclusion bodies is still obscure. They resemble rickettsiæ, but possess an unusual morphology. Some years ago I saw similar structures in smears from a mouse lung infection, from which a pure culture of pleuropneumonia-like organisms was grown. These bodies showed the same fine rings and other forms noticed in those from the urethritis cases and were considered to be characteristic pleuropneumonia-like organisms. Intracellular bodies were not noted in these preparations. Dr. F. M. Burnet, of the Walter and Eliza Hall Institute, Melbourne, also observed identical structures in a mouse infection and made drawings of them. Topley and Wilson[6] reproduced a photograph of a stained smear from a culture of bovine pleuropneumonia, in which the same type of ring forms can be recognized.

Beveridge has cultivated pleuropneumonia-like organisms from material in cases of urethritis, but has not shown that they are associated with the inclusion bodies. Johnston and McEwin found both features present in their cases, but hesitated to draw the conclusion that they were related to one another or to the cause of the disease. The findings in the present series would seem to support such a conclusion; but again definite evidence is lacking. The failure to isolate pleuropneumonia-like organisms does not necessarily exclude them from the lesions, as it is probable that horse serum and agar, the only medium available, was not entirely suited to the exacting growth requirements of these delicate bacteria. Observations on the morphology and growth of the organism of bovine pleuropneumonia and the pleuropneumonia-like group have in the past been concerned chiefly with dark-ground illumination and impression smears of cultures in artificial media, and have indicated the wide range of variation which occurs. The appearance of the organisms in infected tissues and cells has not received much detailed study.

The inclusion bodies may be a separate virus, and they may not be associated ætiologically with the urethritis. Further work is clearly needed to elucidate these points. However, on the basis of the morphological features seen in these cases, it is tentatively suggested that the inclusion bodies represent an intracellular phase of the pleuropneumonia-like organism which has been shown to be present in a proportion of cases of non-gonococcal urethritis.

Summary.

Ten cases of non-gonococcal urethritis in which inclusion bodies were found are reported among troops from the Borneo area. The nature of the inclusion bodies is discussed.

Acknowledgement.

I wish to thank Major-General S. R. Burston, Director-General of Medical Services, for permission to publish this paper.

References.

(1) V. N. B. Willis: "Urethritis in the Male", THE MEDICAL JOURNAL OF AUSTRALIA, September 26, 1942, page 294.

(2) N. Gibson: "Control of Venereal Disease in the Army", THE MEDICAL JOURNAL OF AUSTRALIA, September 26, 1942, page 290.

(3) G. A. W. Johnston and J. McEwin: "Non-Gonococcal Urethritis: Considerations of Ætiology: Findings in Two Cases", THE MEDICAL JOURNAL OF AUSTRALIA, April 14, 1945, page 368.

(4) W. I. B. Beveridge: "Isolation of Pleurnopneumonia-Like Organisms from the Male Urethra", THE MEDICAL JOURNAL OF AUSTRALIA, December 11, 1943, page 479.

(5) W. I. B. Beveridge, A. D. Campbell and P. E. Lind: "Pleuropneumonia-Like Organisms in Cases of Non-Gonococcal Urethritis in Man and in Normal Female Genitalia", in the press.

(6) W. W. C. Topley and G. S. Wilson: "The Principles of Bacteriology and Immunity", 1936, Figure 209, page 742.

CHROMOBLASTOMYCOSIS, WITH REPORTS OF TWO CASES OCCURRING IN QUEENSLAND.

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CHROMOBLASTOMYCOSIS or chromomycosis is a chronic, slowly progressive, fungous disease of the skin. It is one of the varieties of *dermatitis verrucosa* or "mossy foot".

Cultural studies have incriminated several species of fungi. The parasites may readily be detected culturally or histologically in the diseased tissue and distinguished from other pathogenic fungi by their brown pigmentation. It is likely that these fungi are normally saprophytic on wood, dead grass or other vegetation, and that they only occasionally gain entrance to human tissues. This conclusion is supported by the relative infrequence of cases, coupled with their extensive geographical distribution.[1] Cases have been described from Brazil, Uruguay, Argentine, Venezuela, the West Indies, the United States of America (nine cases),[2] Russia, Japan, Java, Algeria, Rhodesia and South Africa. Reports have been more numerous from tropical than from temperate zones. As far as we are aware, no Australian case has previously been reported. (It is true that Strong[3] quotes Breinl as using the term "mossy foot" to refer to a verrucous condition of the lower part of the legs. Breinl,[4] however, was describing a case of elephantiasis.)

Most patients are agricultural workers, and adult males predominate. The lesions are usually found on the limbs. There is frequently a history of some previous trauma, by which apparently the infecting fungus gained access.

The lesion is a granuloma. Clinically it first appears as a small nodule, which increases in size. The centre may heal with scarring. The surface may become scaly or ulcerated, or warty, or papillomatous projections may develop. Other nodules may form in the neighbouring skin. Evolution is slow; patients may give a history of twenty years' duration or more. In cases in which the condition is of long standing and has been neglected (such cases were the first to be described), the limbs may become covered with large, numerous, cauliflower growths. Such cases are well described by Simson *et alii* in South Africa.[1]

The differential diagnosis has to be made from other mycoses, from early carcinoma, from syphilis and from *tuberculosis verrucosa cutis*. The laboratory diagnosis may be made readily in several ways.

1. The brown fungus can be seen microscopically in pus or in scrapings treated with caustic potash.
2. The fungus is evident in histological preparations.
3. The method of choice is to cultivate the fungus from the nodule, for this enables its species to be determined.

The prognosis is good; the disease does not cause death, nor does it spread to the viscera. Some patients (perhaps because they were treated early) have responded readily to large doses of iodide. In other cases the condition has been more resistant. Radiotherapy has also been recommended. Surgical excision is indicated in some cases.

Reports of Cases.

The two cases recorded below show that the disease is present in Australia also.

CASE I.—E.E., a male patient, aged forty-five years, living near Kingaroy, was first examined in September, 1943. He complained of a tumour on the right forearm. He had first noticed it in about 1938; he recalled no previous trauma. The tumour then resembled a wart and had increased slowly in size. It was never painful and was never ulcerated. Hæmorrhage occurred only from trauma—the minor knocks and abrasions of everyday life. The patient had been a stockman all his life. Among his many jobs with cattle and

horses had been that of putting his hand and forearm into the vagina of mares in order to dilate the cervix. This was considered to aid conception.

On examination of the patient was seen a circular tumour, fifteen millimetres in diameter and raised five millimetres above the healthy skin, from which its edges rose perpendicularly. The tumour had a firm elastic consistency (rubbery), not at all like a malignant tumour. It was freely movable on the deep fascia, and no inflammatory or other involvement of the surrounding tissues was present. There was no tenderness. The lymph glands in the epitrochlear, axillary and supraclavicular areas were not palpable.

A provisional diagnosis of a fungous infection was made, and a strong salicylic acid and benzoic acid ointment was prescribed, with instructions to the patient to return in a few weeks. However, the patient did not return until January, 1945. There was now little change in the tumour, except that its height had decreased and its surface was smoother. This effect may have been due to the ointment. At no time was any ulceration or the irregular surface of a warty growth seen. No other skin tumours or ulcers were present.

On February 1, 1945, the tumour was excised under local anæsthesia. About one centimetre of apparently healthy surrounding skin was removed with the growth, and rather more than one centimetre of deep fascia. The wound healed normally.

The tumour, when examined after fixation in formalin, was almost circular, the margin being slightly irregular. Its diameter was fourteen millimetres, and it projected two millimetres above the skin level. The edge rose rather abruptly on one side; on the other it shelved into the skin. The surface was flat and fairly smooth, except for some tiny nodules near the edge. It was not ulcerated. Its colour was that of the normal skin around. When it was cut across, an oval, colourless, translucent mass four millimetres thick was evident in the dermis, immediately beneath the thickened epidermis (Figure I).

Microscopic examination showed the nodule to be a granuloma of the tuberculoid type. Foreign body giant cells were numerous (Figures II and III); some were degenerate, having ill-defined nuclei and strongly eosinophile cytoplasm. There were many foci of epithelioid cells. Polymorphonuclear leucocytes were occasionally massed to form minute abscesses (Figure II). The intervening tissues were thickly infiltrated with cells, mostly lymphocytes, polymorphonuclear leucocytes and plasma cells. Eosinophile cells were numerous and conspicuous. An occasional group of histiocytes contained brown pigment. Fibroblastic reaction was slight. The epidermis was hypertrophied, and lengthened projections from it twisted about in the granuloma (Figure I). Intra-epithelial abscesses were present. The inflammation did not extend into the subcutaneous tissue.

Scattered throughout the granuloma were numerous well-defined fungous cells. They lay singly or in small groups within giant cells (Figures II and III) or tissue spaces. Sometimes several, perhaps as many as eight, were grouped together in the centre of a small abscess (Figure II). The parasites were usually round, sometimes oval. They appeared as thick rings, usually from 8·0μ to 10·0μ in diameter. Occasional forms were as small as 5·0μ or as large as 14·0μ. In unstained sections they were brown; with Giemsa's stain they became green; with Gram's stain they took up the gentian violet, becoming very dark. In some cells the ring had several rounded, dark masses attached to its inner aspect (Figure V), but in many, little or no internal structure could be distinguished. Some of the parasites were irregular, as if disintegrating.

The method of propagation of the parasite was not clearly evident from the histological examination. Occasionally a curved septum was present, suggesting transverse fission (Figure VI). Occasionally a small cell resembling a bud was present beside a large one (Figures II and IV). Rarely one cell seemed to bear to another the relationship of an egg to an egg-cup (Figure VII). No hyphæ were seen. Clearly proliferation had been slow and difficult in the face of tissue resistance, for the lesion was still small after seven years' development. In discussing the reproduction of the parasite, Emmons *et alii*[5] make the following statement: "Septation of spherical or egg-shaped cells is frequent and well developed hyphæ may appear in the superficial crusts. True budding does not occur." Moore and his co-workers[3] also emphasize that budding of these fungi is not a characteristic form of reproduction in tissue.

CASE II.—The patient was a printer, aged sixty years, living at Childers. His was a sedentary life, chopping wood for the household fire being his only exercise. This wood was dry and hard, not rotting. He did not garden.

At about the end of March, 1945, some molten linotype metal splashed on his hand, causing superficial burns. These all healed except one small patch on the dorsum. On the centre of this there formed a dry scale, which habitually fell off, soon to be replaced by another. The edges of the patch were slightly raised and rolled. The edge gradually extended without any increase in the size of the central scaly area. The lesion was suspected to be an epithelioma and was accordingly excised on August 21, after a duration of five months. The wound healed uneventfully. There were no other such lesions on the body surface.

When the excised tissue was received in the laboratory, the lesion was seen to be circular and fifteen millimetres in diameter. An outer zone was white as if from thickening of the epidermis. The central part (about ten millimetres in diameter) was brown and shaggy and elevated about two millimetres above the level of the surrounding skin. When cut across the lesion was seen to be superficial.

Histological examination showed clearly the mossy appearance of the surface. The epidermis was thrown out in projections thickly clothed with keratin and cored with narrow dermal papillæ. In the papillæ were many greenish-brown granules varying in size and distinctness, probably derived from degenerate fungous elements. The rete pegs twisted about and anastomosed, but did not penetrate deeply. The granulomatous tissue occupied the superficial part of the dermis, and the histological picture was the same as in Case I. Parasites were much less numerous, as might perhaps be expected from the much shorter duration.

Comment.

It is possible that chromoblastomycosis is not so rare in Australia as the lack of reports would suggest. The warm, humid climate of the coastal districts of Queensland, especially in the north, might be expected to favour the occurrence of fungous infections. Cases of dermal mycoses are, in fact, common.

It is not likely that Australian medical practitioners will encounter the advanced, untreated type of "mossy foot" with large excrescences. Rather would any patients be expected to present themselves while the lesion was a comparatively small nodule, as in the present examples.

No cultural studies were undertaken in our cases, as the material was fixed in formalin. Therefore, no report can be offered as to the species of infecting fungus.

Summary.

1. Two cases of chromoblastomycosis are described.

2. In each case the lesion was a small granuloma in the skin of an adult male—in one on the forearm, in the other on the hand.

3. The possibility of chromoblastomycosis should be considered in the differential diagnosis of small masses in the skin. Unless the possibility is kept in mind, the condition is likely to be mistaken for early squamous carcinoma.

Acknowledgements.

We are indebted to Dr. J. Coffey, Deputy Director-General of Health and Medical Services, Queensland, for permission to publish this paper. For the photomicrographs we are grateful to Professor H. J. Wilkinson. Professor J. B. Cleland was good enough to trace the reference to Breinl's work quoted by Strong. The histological material was prepared by Mr. P. G. McMahon, B.Sc.

Legends to Illustrations.

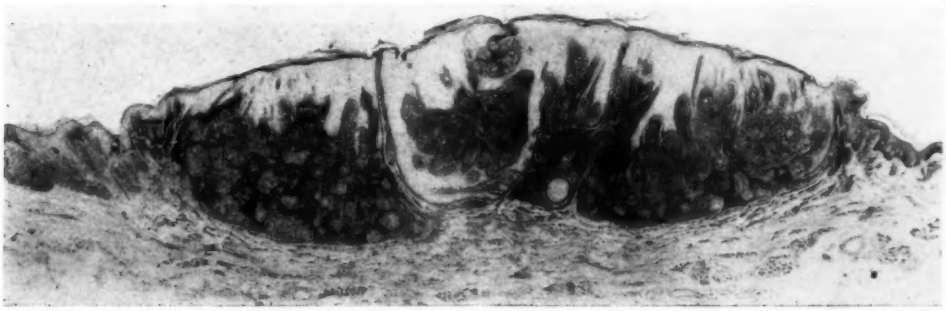
FIGURE I.—Chromoblastomycosis. Cross-section of the whole lesion showing granulomatous nodule in the dermis and hypertrophy and downward projections of the epithelium. (Giemsa stain, × 8.)

FIGURE II.—On left giant cell (G) containing a fungous cell. On right a micro-abscess in which two cells are evident; to one is attached a structure like a bud; two other fungous cells are out of focus. Eosinophile leucocytes at E. (Hæmatoxylin and eosin stain, × 990.)

FIGURE III.—Three fungous cells in a giant cell. (Giemsa stain, × 760.)

FIGURE IV.—Group of fungous cells. The largest cell shows evidence of septation. The smallest suggests a bud. (Giemsa stain, × 1,730.)

ILLUSTRATIONS TO THE ARTICLE BY Dr. W. J. SAXTON, Dr. F. HATCHER AND Dr. E. H. DERRICK.



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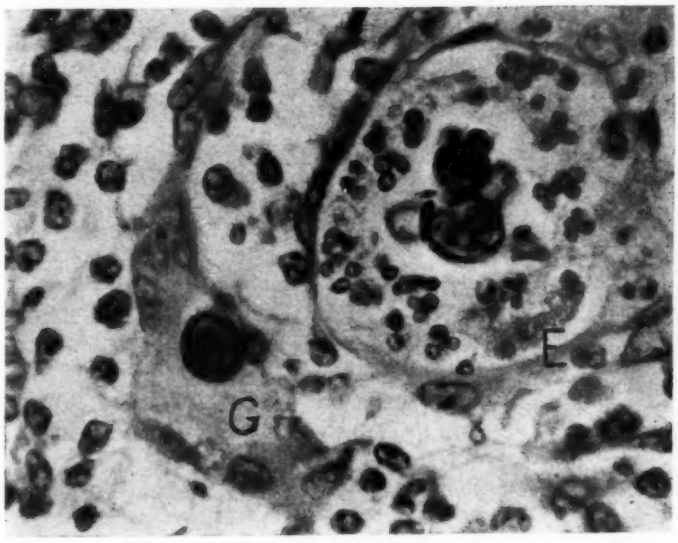

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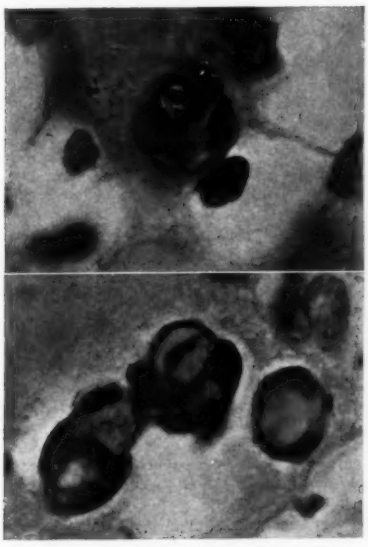

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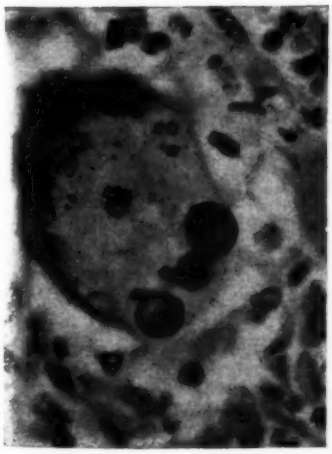

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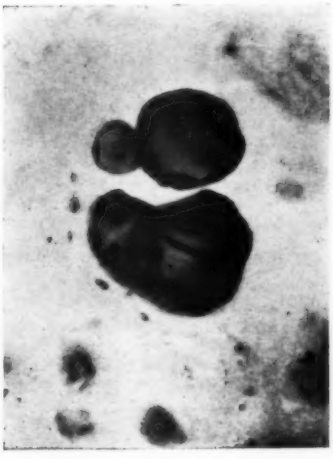

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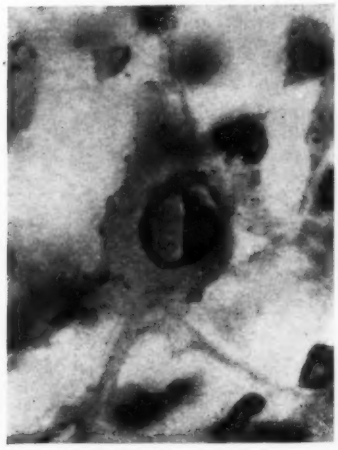
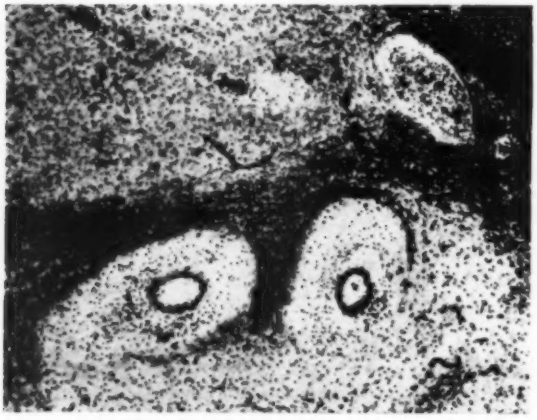


FIGURE VI.

ILLUSTRATIONS TO THE ARTICLE BY Dr. CHARLES SWAN.



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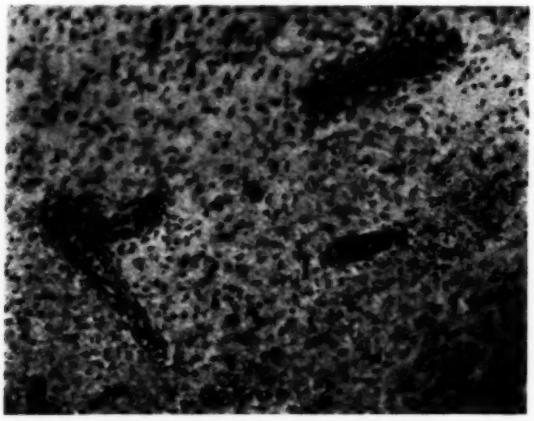

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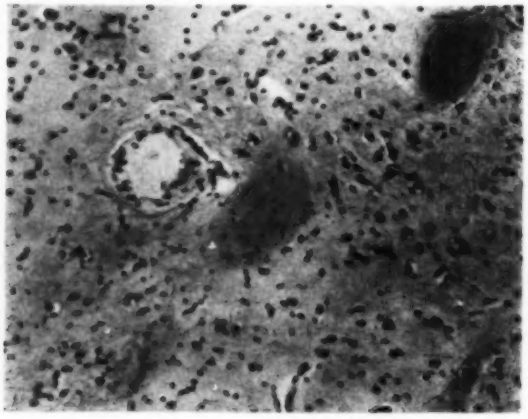

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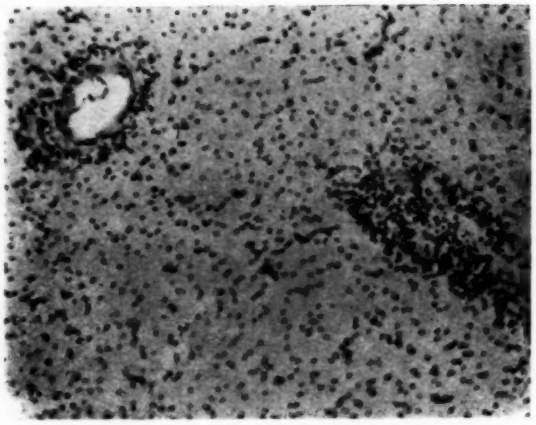

Figure IV.

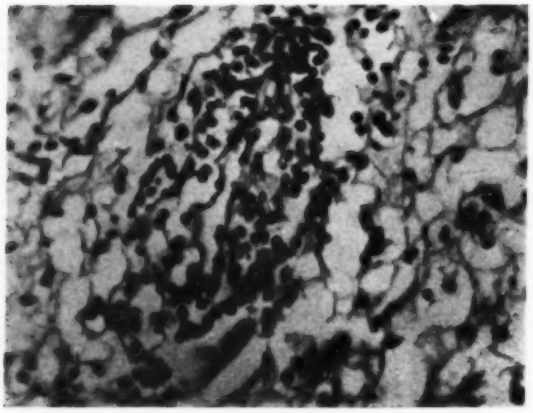

Figure V.

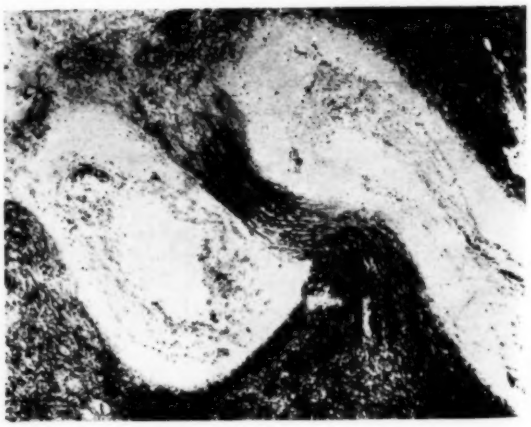

Figure VI.

FIGURE V.—Composite photomicrograph. Above: a fungous cell showing three dark, rounded masses projecting inward from its circumference. Below: curious "egg in egg-cup" appearance of fungous cells within a giant cell. (Hæmatoxylin and eosin stain, x 1,560.)

FIGURE VI.—A fungous cell (which is enclosed within a large macrophage) showing a septum and a dark internal mass. (Hæmatoxylin and eosin stain, x 1,560.)

References.

(1) F. W. Simson, C. Harington and J. Barnetson: "Chromoblastomycosis: A Report of Six Cases", *The Journal of Pathology and Bacteriology*, Volume LV, April, 1943, page 191.

(2) M. Moore, Z. K. Cooper and R. S. Weiss: "Chromomycosis (Chromoblastomycosis): Report of Two Cases", *The Journal of the American Medical Association*, Volume CXXII, August 28, 1943, page 1237.

(3) R. P. Strong: "Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases", Sixth Edition, 1942, page 1190.

(4) A. Breinl: "Australian Institute of Tropical Medicine: Report for the Year 1910", page 18.

(5) C. W. Emmons, H. Hailey and H. Hailey: "Chromoblastomycosis: Report of the Sixth Case from Continental United States", *The Journal of the American Medical Association*, Volume CXVI, January 4, 1941, page 25.

Reports of Cases.

A CASE OF POST-VARICELLAL ENCEPHALITIS SHOWING BILATERAL SOFTENING OF THE NEOSTRIATUM AND TERMINAL "TETANOID CHOREA" (GOWERS).

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INVOLVEMENT of the nervous system as a complication of varicella is not uncommon. Up to 1939 Bergman and Magnusson[1] were able to collect approximately 150 cases from the literature; to these they added 10 cases of their own. The prognosis is moderately good; of 126 cases cited by these investigators, in 91 complete recovery occurred, in 17 recovery was partial, in two no improvement took place, and in 16 the patient died (a mortality rate of 12·7%).

Few accounts of the pathological changes in the nervous system have been recorded; those appearing up to 1935 have been summarized by Underwood.[2] Owing to the lack of uniformity of these reports, Waring, Neubuerger and Geever[3] doubt ". . . whether a typical histologic picture of 'encephalitis varicellosa' can be established". Omitting non-specific changes, these authors consider that there are only four cases in the literature in which lesions in the nervous system resemble those seen in their own. The cases they cited included those of van Bogaert,[4] Zimmerman and Yannet,[5] Dagnelie and Dubois,[6] and Bergman and Magnusson. On the basis of the two cases with the fullest description of the neuropathology[4,5] Van Rooyen and Rhodes[7] believe ". . . that demyelination is the characteristic feature, but as so few cases have been fully investigated it would be unwise to conclude that no other type of lesion may occur".

The present case is of considerable interest, not only because the histo-pathological findings differed somewhat from those previously published, but also because the confinement of the main lesion to the neostriatum afforded a unique opportunity for study of the effect of abrogation of its function.

CLINICAL RECORD.

The following account is based on the case notes taken at the Adelaide Children's Hospital and on a personal interview with the father about eighteen months after the patient's death.

R.J.P., a boy, aged six and a half years, was admitted to the Adelaide Children's Hospital on December 12, 1943, under the care of Dr. E. Britten Jones. Prior to his illness he had been a normal, healthy child. At the age of five years he had been inoculated against diphtheria without untoward effect. He had never suffered from urticaria, asthma, hay fever or jaundice. His sister, aged ten months, was healthy. The house in which he lived was clean and free from rats and mice.

A fortnight before his admission to hospital, the patient had contracted chicken-pox. At the time of onset of the eruption he had complained of a sore throat. About a week later his father had noticed that occasionally while talking to him the boy would clench and unclench his fists for a few seconds, ". . . then he seemed all right again". At about the same time he had complained of abdominal pains. On the day afterwards he said that he felt "rotten" and was "sore all over". The father considered that at this stage his disposition had altered. For about five days before his admission to hospital he was sleepy; when he woke up he looked "vacant or as if he had had a bad dream". (In retrospect, the father believes that the boy probably had at this stage of his illness what was a convulsive seizure lasting about ten minutes.) On the night before his admission to hospital the patient had visual hallucinations and saw tigers, snakes and elephants sitting on his pillow. He also complained of severe headache. On the morning of the day of his admission he appeared normal. Soon after he had been given his lunch to eat, he was found sitting up rigidly in bed, with his hands clutching tightly at the sheets, his eyes bulging and vacant-looking, his mouth full of food, and food streaming out of his nostrils. His limbs and face twitched, mucus poured from his mouth and he became blue.

On his admission to hospital the child was unconscious, his limbs were in a state of tonic spasm and his head was retracted. His mouth and eyes were moving and he was biting his tongue. He was cyanosed and mucus was running out of his mouth. His temperature was 99·8°F., his pulse rate was 120 per minute and his respirations numbered 24 per minute. His pupils reacted sluggishly to light. There was no neck rigidity. Rhonchi were present all over the lung fields. The tendon reflexes of both upper and lower limbs were equal and active. The plantar reflexes were "doubtful extensor" in type. The boy seemed irritable; tonic spasms occurred as soon as he was touched. A provisional diagnosis of encephalitis after chicken-pox was made.

After an intramuscular injection of two grains of phenobarbital the child became much quieter, and no further spasms occurred. Lumbar puncture yielded clear cerebrospinal fluid under slightly increased pressure. It contained 16 lymphocytes per cubic millimetre, and 720 milligrammes of chlorides and 25 milligrammes of protein per 100 cubic centimetres; sugar was present; the amount of globulin was not increased. The fluid was sterile on attempted culture.

During the night the boy was fairly comfortable. Muscular spasms occurred most of the time he was awake. He took small amounts of fluid willingly.

Next morning the patient was restless and agitated. He complained of a sore throat and headache. Later his condition improved; he spent a comfortable day and for the most part slept well during the night.

Examination on December 14, disclosed that the child responded satisfactorily to requests. His knee and ankle jerks could not be elicited. The superficial abdominal reflexes were present and the plantar reflexes were flexor in type. The pupils reacted to light, but oscillated (hippus).

On December 17 the boy showed no improvement. Some flattening of the left side of his face was observed and his smile was uneven. The tendor reflexes were still absent. The plantar reflexes were variable. In view of the possibility that the case might be one of infectious polyneuritis, it was decided to watch the patient closely for respiratory distress, so that if the necessity arose he could be placed in a respirator. During the day the patient had some attacks in which he cried out and drew up his legs as if in pain. Except for similar attacks he had a fairly comfortable night. From time to time he cried in his sleep.

[1] Work done with the aid of grants from the National Health and Medical Research Council and the Keith Sheridan Research Fund of the University of Adelaide.

On December 18 the child's condition was worse and he had further spasms. He was placed in a respirator, but as there was no improvement he was soon removed. In the afternoon he was visited by his father and was able to wave good-bye.

On the following day the patient's condition was unchanged. At intervals he dozed off into a sleep from which he awakened with a shrill cry. Then he drew up his knees, arched his back and retracted his head; in addition his arms became stiff. During each attack he moaned continuously. In the afternoon the spasms were more severe and more frequent; two drachms of *Haustus Chloralis* were given. The boy was fairly quiet until 9.30 p.m. when he had further attacks in which he was noisy. At 11.45 p.m. one-sixteenth of a grain of morphine was given without effect. At 1 a.m. one grain of phenobarbital was given and he became quiet. Even in his sleep, however, the patient continued to move his limbs at intervals.

Spasms similar to those described occurred throughout the remainder of the child's illness. They became more severe and more frequent. The attacks lasted from two to ten minutes and at times were almost continuous. They were especially severe at night.

On December 21, a drug rash, attributed to bromide or phenobarbital, was present; administration of these drugs was therefore discontinued. On lumbar puncture approximately 15 cubic centimetres of clear cerebro-spinal fluid under increased pressure were withdrawn. Examination of the fluid disclosed 20 leucocytes per cubic millimetre, all of which were lymphocytes; the fluid contained 720 milligrammes of chlorides and 20 milligrammes of protein per 100 cubic centimetres; sugar was present; the amount of globulin was not increased; no microorganisms were detected on attempted culture.

Except on the day of his admission to hospital, until December 22 the patient's temperature had never risen above 100° F. and on only three occasions above 99° F. His maximum temperature on December 22 was 103° F. at 10 p.m. At this time his pulse rate was 160 per minute and his respirations numbered 48 per minute.

On December 23 the child was restless and was having frequent spasms. Attempts were made to control them by the administration of morphine and of paraldehyde. In the evening the temperature was 105° F., the pulse rate was 144 per minute and the respirations numbered 28 per minute. Sponging reduced the temperature to 101° F. At 1.15 a.m. the boy's temperature was 105° F., his pulse was uncountable and his respirations numbered 48 per minute; his temperature rose to a similar level at 3.30 a.m. and again at 5.40 a.m. Attempts were made to control his temperature by sponging and by the application of ice-packs to his head and neck. The spasms were almost continuous and were associated with severe tremor. In the morning the patient was exhausted. His breathing was noisy owing to the accumulation of mucus in the upper respiratory tract.

On December 24, on account of the pulmonary condition, the boy was ordered 1/150 grain of atropine as required. The severe spasms continued and left the patient thoroughly exhausted. The attacks were associated with profuse sweating, tremors and crying out. Head retraction was more pronounced.

On December 25 the child's condition was worse. At 1 p.m. he had a particularly severe spasm in which his temperature rose to 106° F. Six tablets (three grammes) of sulphathiazole were given. At 6 p.m. the temperature was 105° F., the pulse was uncountable and the respirations numbered 72 per minute. During the night the patient was given one grain of phenobarbital intramuscularly at 8.20 p.m. and again at 1.45 a.m. In an effort to combat the accumulation of secretion in the upper air passages, hypodermic injections of 1/100 grain of atropine were given at 10.20 p.m., 1.45 a.m. and 4 a.m. At 4 a.m., because of difficulty in respiration, the boy was placed face downwards over pillows, with considerable improvement. Although the child was sponged several times during the night, on the three occasions at which the temperature was taken it was higher than 105° F., the corresponding pulse and respiratory rates being about 160 and 70 per minute, respectively.

At 8.30 a.m. on December 26 the patient's breathing was laboured and his pulse was imperceptible. Death occurred at 8.40 a.m.

POST-MORTEM EXAMINATION.

Unfortunately the autopsy notes are not available. It would appear, however, that apart from the cerebral condition, the only abnormality observed was bronchopneumonia.

Central Nervous System.

On macroscopic examination, externally the brain appeared to be normal. After fixation in 10% formol-saline solution, examination of frontal slices of the cerebrum disclosed that in each hemisphere the region of the basal ganglia was softer in consistence than the remainder of the brain.

Microscopic examination gave the following results.

Cerebrum.—In the meninges, infiltration of the pia-arachnoid was slight. Scattered collections of cells were observed, mainly in the depths of sulci and adjacent to blood vessels. The cells comprised lymphocytes and adventitial cells together with a few polymorphonuclear leucocytes. Occasionally red blood corpuscles were also present.

Within the central nervous system the brunt of the pathological process was borne by certain portions of the grey matter of the *corpus striatum*. The lesions were characterized by diffuse softening, usually greatest in degree immediately adjacent to blood vessels (Figure I). These changes were associated with a reaction on the part of the interstitial tissues, including congestion and œdema, and extraadventitial, perivascular and tissue infiltration.

In the most severely affected regions, softening was pronounced and the imminence of liquefaction was evidenced by the appearance of minute spaces in the brain substance, giving it a spongy appearance. (Sections through such areas tended to tear on being cut even though the material was embedded in celloidin.) In addition, sometimes complete disintegration of nervous tissue had taken place in the perivascular zones, leaving a gap between the vessel wall and the brain substance, often bridged by delicate collagen fibrils laid down by the cells of the adventitia. Where the process was less intense the vessels were surrounded by cuffs of softening or of demyelination; together with the vessel these cuffs measured in diameter about three times that of the vessel alone.

In the involved areas there was considerable loss of nerve cells. Remnants of some appeared as palely-staining nuclei without nucleoli or cytoplasm; other cells were shrunken and sclerotic. In less severely affected neurones were seen degenerative changes including swelling of the cell, chromatolysis and nuclear and nucleolar eccentricity.

Many of the nerve fibres had also undergone disintegration; in Weil-Weigert preparations, however, remnants of some of the myelin sheaths appeared as pale-blue granular debris, and in other sheaths fragmentation, tortuosity, beading and vacuolation were present. The axis cylinders (Bielschowsky and Foot preparations) likewise were necrotic or affected by degenerative changes similar to those of the myelin sheaths. It is important to note, however, that many bundles of nerve fibres passing through such areas—as, for example, fasciculi belonging to the internal capsule—were well preserved.

In the most severely affected zones the neuroglial cells of ectodermal origin had also disappeared; where the pathological process was less intense, the astrocytes were swollen and their nuclei dislocated peripherally (*gemästete* cells). Alzheimer cells were also present. The nuclei of the oligodendroglia were surrounded by haloes, indicating that swelling of these cells was present.

The intensity of the tissue infiltration ran *pari passu* with the severity of the parenchymatous changes. Where these were intense there was an enormous increase of cells, the nervous tissue being literally packed with

polymorphic microglial cells in various stages of transformation into compound granular corpuscles (Figures II and III). The *Gitter* cells and occasionally their precursors the rod cells contained numerous globules of lipoid staining scarlet with Scharlach R.

The blood vessels were surrounded by cuffs of inflammatory cells (Figure IV). Often these cells had overflowed from the perivascular sheaths into the adjacent nervous tissue, thus producing extraadventitial infiltration. The cells of the infiltrate were mainly lymphocytes together with a moderate number of adventitial cells (Figure V). In addition there were occasional eosinophile (less often neutrophile) polymorphonuclear leucocytes and plasma cells; sometimes a few of these cells were seen also in the tissue infiltrate. Arteries were affected as much as veins. Although most of the endothelium was normal, occasionally the endothelial cells were swollen. Thromboses were absent. Hæmorrhages were extremely uncommon, but in a few instances escape of a few red blood corpuscles had occurred.

With regard to the distribution of the lesions within the *corpus striatum*, the most severe changes were encountered in the putamen and caudate nucleus; the corpora of the right and left cerebral hemispheres were approximately equally affected. The lesions diminished in intensity as the ganglia were traced caudally. For example, in the heads of both the right and left caudate nuclei the process had reached the pre-liquefactive stage of softening. On the other hand, in the tail of the right nucleus in the roof of the inferior horn of the lateral ventricle, lesions were limited to a few vessels with mild perivascular infiltration and to transformation of the microglia to "rod" cells; in the tail of the left nucleus at a similar level changes were absent. Even in the same section, however, in both the caudate nucleus and the putamen, some areas were relatively better preserved than others. For instance, in the right caudate nucleus the ventral two-thirds were more affected than the dorsal third, and the process was more advanced laterally than medially.

On each side, most of the *globus pallidus* was free from lesions. At one level in the right *globus pallidus* there was a minor degree of softening limited to a small area, while in the left *globus pallidus* there were a few vessels with perivascular infiltration. In general, on each side the internal capsule was well preserved. The grey matter intermingled with it, however, was often affected by degenerative changes or necrosis.

In the cortex, lesions similar to those described in the putamen and caudate nucleus, but slightly less intense, occurred only in the right middle frontal gyrus and the right insula. Elsewhere in the cerebral cortex the pathological process was limited to moderate or mild perivascular infiltration. The changes were observed in all four lobes—namely, frontal, parietal, temporal and occipital. Only occasional vessels were affected. Usually the perivascular infiltration occurred in the deeper cortical laminæ; sometimes it could be traced into the subjacent white matter. In a few regions (notably in the right superior frontal gyrus) vessels affected by perivascular œdema were seen.

In the white matter, a few vessels of the *centrum semiovale* (more so in the right hemisphere) showed mild or moderate perivascular infiltration. Around others there was perivascular œdema. A few scattered vessels were surrounded by thin zones of perivascular demyelination and its concomitant change—namely, extra-adventitial infiltration.

Vessels affected by moderate perivascular demyelination were present in the *fasciculus occipito-frontalis superior* (Figure VI).

In the claustrum, in occasional vessels moderate perivascular demyelination and extraadventitial infiltration were seen. In some instances lesions were confined to perivascular infiltration. Similar changes were observed in the immediately adjacent white matter—namely, that of the insula and that comprising the external capsule.

In both right and left thalami a few neurones were affected by slight degenerative changes (swelling and nuclear eccentricity). In each thalamus a vessel with mild perivascular infiltration was noted.

In the hypothalamus there were a few vessels affected by perivascular infiltration, and one affected by extra-adventitial infiltration.

In the lateral geniculate body on the left side, in three vessels mild perivascular cuffing was present.

In the rhinencephalon, occasional vessels affected by moderate perivascular infiltration were present in the amygdaloid nucleus and uncus.

In the *corpus callosum*, in a few vessels to the left of the mid-line, mild perivascular infiltration was observed.

The optic chiasma, optic tracts, chorioid plexuses and infundibulum were all free from lesions.

Brain Stem and Spinal Cord.—Except for two vessels in the right *substantia nigra* in which mild perivascular infiltration was present, the mid-brain was normal.

In the pons and *medulla oblongata*, in a few vessels in the ventral part of the pons mild perivascular cuffing was present. In the motor cells of the fifth nerve slight chromatolysis was found.

In the thoracic region of the spinal cord, in one vessel in the grey matter mild perivascular infiltration was noted. In the lumbar region, a few anterior horn cells were affected by slight degenerative changes.

Attempts to Transmit the Disease to Animals.

A rabbit and six mice were inoculated intracerebrally with suitable doses of a 10% suspension of glycerinated brain substance, with negative results.

Discussion.

On the basis of a series of 120 cases culled from the literature, Underwood[2] found, as might be expected from the age-incidence of chicken-pox, that post-varicellal encephalitis is predominantly a disease of children; 85% of his patients were aged less than ten years. Males are affected more often than females; 69 of 112 patients[2] were males. In most instances the time that elapses between the appearance of the rash and the onset of neurological complications is from four to ten days. The present case conforms to these findings, in that the patient was a male, aged six and a half years, who manifested nervous symptoms seven days after the onset of the eruption.

In the present instance the duration of the illness, from the onset of nervous sequelæ until death occurred, was three weeks; in earlier cases,[4][3][1][5] confirmed pathologically, the intervals were respectively seventeen days, six days, one day and one day.

In nine fatal cases Underwood states that the lowest temperature recorded[2] was 99·5° F. and the highest[2] was 107° F.; usually it ranged between 102° and 104° F. In the present case the highest temperature recorded was 106° F.

On the first occasion on which lumbar puncture was performed, the cerebro-spinal fluid was under slightly increased pressure and contained 16 lymphocytes per cubic millimetre. On the second occasion the fluid was still under pressure and the lymphocytes numbered 20 per cubic millimetre. In keeping with these findings, Underwood[2] found that an increase in pressure of the cerebro-spinal fluid occurred in about 50% of cases; in half of these the increase was considerable and in the remainder it was slight. There was a pleocytosis (usually slight) in 24 out of 55 cases; in the vast majority in the cell content there was a preponderance of lymphocytes or mononuclear leucocytes.

The terminal symptomatology in the case here recorded is extremely unusual. However, because of the situation of the main lesions in the nervous system, it seemed reasonable to assume that the signs and symptoms would resemble those referable to the nervous system in an advanced stage of hepato-lenticular degeneration (Wilson's disease)[2]. In conformity with this assumption the initial symptomatology included clenching and unclenching of the fists (perhaps athetoid movements), alteration in personality, rigidity and clutching at the sheets. The last-

mentioned phenomenon was observed also in the case of Howard and Royce[9].

On reading the paper of Barnes and Hurst,[10] I was immediately struck by the great resemblance of the nervous symptomatology of the present case to that in their Case I. Their patient was readmitted to hospital on October 6, 1924, on account of bronchopneumonia and an accentuation of his spasms. Barnes and Hurst's description is so vivid that it is well worth quoting in full,

> During this febrile period, a change had come over his general nervous condition. The rigidity was as pronounced as before, but now, and especially during the last few hours of his life when the temperature was considerably raised, he suffered greatly from a series of severe and generalized spasms, closely resembling those seen in tetanus. He lay in bed in an extended position, completely conscious but unable to articulate more than a mere gurgle; no word he attempted to utter was comprehensible. He sweated freely and his facial expression was one of pain and fright. His usual rigidity was now intensified by the spasms which occurred every fifteen seconds or so, and which subsided only partially after some five seconds. The trunk muscles were rigid throughout, so that any attempt at passive movement (which tended, as in tetanus, to increase his spasm) resulted in him being moved *en bloc* without any of the normal suppleness of the trunk and limbs. His neck was slightly flexed, all the muscles, and especially the sternomastoids, being in strong tonic contraction. His jaws were clenched in such a way that the upper incisor teeth indented his lower lip, whilst the upper lip was everted and the angles of the mouth drawn down. The abdominal muscles were in such intense spasm that palpation of viscera was out of the question; the recti stood out sharply. Spontaneous movements of the legs occurred as part of the generalized spasms, the limbs being drawn up (flexed at the hip) and the feet strongly extended (plantar-flexed) on the legs. Similar spasms occurred in his arms, which were rigidly adducted to the trunk; a small degree of movement, from the fully extended to the slightly flexed postures, occurred at the elbow-joint during the spasms. The forearms were powerfully pronated, especially during the spasms, whilst spasm of the *flexor carpi ulnaris* caused the hand to be deviated at the wrist to the ulnar side. His hands were tightly clenched, more so during the spasms; even when partly relaxed it was not possible, passively or voluntarily, to extend his fingers or open his hands without causing general spasm and intense pain.
>
> A tonic spasm, which never fully relaxed, caused flexion of the hips and knees. During the acme of his attacks the legs were lifted completely off the bed. Any attempt to straighten the limbs passively caused great distress; his back was arched (lordosis) and the head was retracted at the same time. Adductor spasm in the thighs caused the limbs to remain crossed throughout this period. His feet were in the equino-varus position, intensified during the spasm but never relaxing to the normal position; the toes were strongly flexed.
>
> It was just possible to obtain knee-jerks and ankle-jerks between the spasms; the left plantar reflex was flexor and the right extensor in type.
>
> His optic discs and pupil reflexes were normal. He had no pigmentation of Descemet's membrane. The ocular movements were normal in all respects. Swallowing was possible with difficulty; he was totally unable to masticate.
>
> The spasms increased in severity on the evening of October 6, and caused him to make cries of pain. Breathing was more difficult. After a small dose of morphia he improved, the spasms nearly ceasing; rigidity was still strongly marked throughout. On October 9 the spasms recurred, being very severe in arms and legs; later the right side of the face was also involved; he sweated profusely during the attacks. He died at 4 a.m. on October 11, 1924.

In all essential details the clinical picture in the two cases is identical, and it is obvious that we are dealing with a condition first described by Gowers[11] under the title of "tetanoid chorea". Similar cases have been described by Ormerod[12] and Homén.[13] It is of considerable interest that in the case of Barnes and Hurst, as in the present case, the main damage fell upon the neostriatum. On the other hand Ormerod detected lesions only in the lenticular nuclei, while Gowers found no lesions in the central nervous system. Both the last-mentioned authors, however, recorded their cases during the latter part of the last century, when neuro-pathological technique was in its infancy.

Wilson's disease is largely one of adolescence and sometimes runs an acute course. Howard and Royce, for instance, described a case of only five and a half weeks' duration. In the present case, therefore, the possibility had to be considered that the chicken-pox might have led to an exacerbation of a previously undiagnosed Wilson's disease. Against it were the previous good health of the patient, the absence of jaundice, and finally, the normal appearance of the liver on microscopic examination.

Pathologically, the main lesions consisted of diffuse and perivascular softening of the neostriatum, with lesser changes in the right middle frontal gyrus and right insula and relative sparing of the white matter. In view of the variation in the pathological changes from those described earlier, it might be argued that in the present case the pathogenesis was different. However, the fact that in the areas of softening the most intense changes occurred perivascularly, and the observation that perivascular demyelination was detectable in the *fasciculus occipito-frontalis superior* and in a few instances elsewhere in the white matter, suggest that in all the cases the basic mechanism is the same, and that the lesions differ from those recorded previously only in location and intensity. In this regard, Hurst's[14] studies on experimental demyelination show that it is possible to produce by varying doses of a single agent, a continuous series of changes ranging from necrosis on the one hand to demyelination on the other.

With regard to the ætiology of post-varicellal encephalitis, five main hypotheses have been propounded. I shall deal with these *seriatim*:

1. That the occurrence of encephalitis in relation to chicken-pox may be a mere coincidence.

Wilson[3] refers to cases of lenticular degeneration in which cirrhosis of the liver was absent. Hurst[14] lists cases of bilateral necrosis in the basal ganglia ascribed to such diverse causes as poisoning by carbon monoxide and by cyanide, the administration of anæsthetics, overdosage with morphine and barbiturates, cerebral trauma and pneumonia. (Incidentally, Hurst[14] has succeeded in producing bilateral softening of the neostriatum in the monkey by the administration of sodium azide.) In view of these findings, were the case here described an isolated example, it would be permissible to consider its association with varicella as being purely fortuitous. In favour of the contrary view, however, is the fact that cases of post-varicellal encephalitis[3][15][16] ("choreo-athetotic" forms) have been reported which must have had a pathological basis similar to that of the present case. Moreover, in the present case, the time interval between the onset of the rash and the occurrence of the neurological complications conforms to the average of earlier cases.

2. That the nervous condition may result from infection with the viruses of known diseases such as poliomyelitis and *encephalitis lethargica*.

Against this hypothesis is the fact that in their symptomatology and in the distribution and character of the neuropathological changes, these diseases[17][18] bear little resemblance to post-varicellal encephalitis.

3. That the disease develops subsequent to the activation by the varicellal infection of a virus lying latent in the tissues.

As I pointed out earlier,[19] the negative results of animal inoculation experiments fail to substantiate this possibility, unless it is assumed that the virus is specific for man only.

Furthermore, Underwood maintains that if this hypothetical virus was the cause, it would be reasonable to assume that the mortality rates of encephalitis occurring after the exanthemata and subsequent to vaccination would be similar, whereas in point of fact they are different.

4. That the condition is caused by the direct action of the virus of chicken-pox on the central nervous system.

Oppenheimer[30] reported a case of congenital chickenpox, in which widespread necroses associated with intranuclear inclusion bodies were found in the skin and viscera; although no lesions were detected in the central nervous system, it seems fair to expect that had lesions been present they would have been accompanied by inclusion bodies. Admittedly, in the present case the state of preservation of the brain rendered critical histological investigation difficult. Nevertheless, despite careful search, no inclusion bodies were seen, and consequently it was considered unlikely that the lesions were due to the direct action of the virus of varicella on the nervous parenchyma.

5. That the complication is allergic and is due to a local anaphylactic reaction on the central nervous system.

From the fact that in disseminated sclerosis and related conditions the initial lesion is perivascular demyelination, Dawson[31] and others[32][33] concluded that the causal agent was diffused through the walls of the blood vessels. It is generally accepted that in anaphylactic phenomena the resultant tissue injury leads to the liberation of a histamine-like substance. As histamine increases the permeability of blood vessels, it would seem logical to believe that the pathogenesis of the various demyelinating diseases might be explained on similar lines. The evidence with regard to this hypothesis has recently been reviewed by Hurst.[34] To some extent it is supported clinically by the observations of Kennedy[35] and experimentally by the work of Jervis.[36] But even if we accept the hypothesis, we are still far from understanding why some vessels should be rendered permeable while others are spared. Furthermore, what is the nature of the myelinoclastic factor? Is it the histamine-like substance itself, is it an agent in character similar to or identical with complement which normally circulates in the blood-stream and which ordinarily is prevented from reaching the nervous tissue by the integrity of the blood-brain barrier, or is it a factor which is present in only a proportion of people?

Finally, if the basic mechanism is the breaching of the hæmato-encephalic barrier, may not some cases be due to the direct action of the virus on the blood vessels such as obtains in infectious myxomatosis of rabbits,[37][38][39] and in other virus diseases?[20][21] It is conceivable, too, that the entrance of a "spreading factor" into the circulation may lead to a similar breakdown.

SUMMARY.

Seven days after the development of the rash of chickenpox, a boy, aged six and a half years, showed signs and symptoms indicative of involvement of the nervous system, which terminated in a condition of "tetanoid chorea". Death occurred from exhaustion and bronchopneumonia three weeks after the onset of the nervous sequelæ. Pathologically the main lesion was bilateral softening of the neostriatum. The pathogenesis of the condition is discussed.

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REFERENCES.

(1) R. Bergman and J. H. Magnusson: *"Studie über Enzephalitis bei Varizellen mit besonderer Berücksichtigung der Spätprognose"*, *Acta Pædiatrica*, Volume XXVI, 1939, page 31.
(2) E. A. Underwood: "The Neurological Complications of Varicella: A Clinical and Epidemiological Study", *The British Journal of Children's Diseases*, Volume XXXII, 1935, page 83.
(3) J. J. Waring, K. Neubuerger and E. F. Geever: "Severe Forms of Chickenpox in Adults. With Autopsy Observations in a Case with Associated Pneumonia and Encephalitis", *Archives of Internal Medicine*, Volume LXIX, 1942, page 384.
(4) L. van Bogaert: *"Histopathologische Studie über Encephalitis nach Windpocken (Encephalitis post Varicellosa)"*, *Zeitschrift für die gesamte Neurologie und Psychiatrie*, Volume CXL, 1932, page 201.
(5) A. M. Zimmerman and H. Yannet: "Nonsuppurative Encephalomyelitis Accompanying Chickenpox", *Archives of Neurology and Psychiatry*, Volume XXVI, 1931, page 322.
(6) J. Dagnelie and R. Dubois: *"Complications neurologiques des exanthèmes (rougeole, varicelle et scarlatine). Protocoles cliniques et anatomopathologiques"*, *Journal de Neurologie et de Psychiatrie*, Volume XXXII, 1932, page 630.
(7) C. E. Van Rooyen and A. J. Rhodes: "Virus Diseases of Man", First Edition, 1940, page 252.
(8) S. A. K. Wilson: "Progressive Lenticular Degeneration", "Neurology", First Edition, 1940, Volume II, page 806.
(9) C. P. Howard and C. E. Royce: "Progressive Lenticular Degeneration Associated with Cirrhosis of the Liver (Wilson's Disease)", *Archives of Internal Medicine*, Volume XXIV, 1919, page 497.
(10) S. Barnes and E. W. Hurst: "Hepato-lenticular Degeneration", *Brain*, Volume XLVIII, 1925, page 279.
(11) W. R. Gowers: "A Manual of Diseases of the Nervous System", Second Edition, 1893, Volume II, page 709.
(12) J. A. Ormerod: "Cirrhosis of the Liver in a Boy, with Obscure and Fatal Nervous Symptoms", *St. Bartholomew's Hospital Reports*, Volume XXVI, 1890, page 57.
(13) E. A. Homén: *"Eine eigenthümliche bei drei Geschwistern auftretende typische Krankheit unter der Form einer progressiven Dementia in Verbindung mit ausgedehnten Gefässveränderungen (wohl Lues hereditaria tarda)"*, *Archiv für Psychiatrie und Nervenkrankheiten*, Volume XXIV, 1892, page 191; cited by S. Barnes and E. W. Hurst, *loco citato*.
(14) E. W. Hurst: "Experimental Demyelination of the Central Nervous System. 3. Poisoning with Potassium Cyanide, Sodium Azide, Hydroxylamine, Narcotics, Carbon Monoxide, Etc., with some Consideration of Bilateral Necrosis occurring in the Basal Nuclei", *The Australian Journal of Experimental Biology and Medical Science*, Volume XX, 1942, page 297.
(15) M. L. H. S. Menko: *"Choreiforme Bewegungen nach Varicellen"*, *Deutsche medizinische Wochenschrift*, Volume XXV, 1899, page 744.
(16) M. Sendrail and O. Dudevant: *"Les formes choréo-athétosiques de l'encéphalite varicelleuse"*, *Bulletins et mémoirs de la Société médicale des hôpitaux de Paris*, Volume XLVIII, 1932, page 358.
(17) C. Swan: "The Anatomical Distribution and Character of the Lesions of Poliomyelitis. With Special Reference to the Type of Cell Affected and to Portal of Entry of the Virus", *The Australian Journal of Experimental Biology and Medical Science*, Volume XVII, 1939, page 345.
(18) J. B. Neal: "Encephalitis. A Clinical Study", First Edition, 1942, pages 137 and 391.
(19) C. Swan: "A Case of Idiopathic Acute Disseminated Encephalomyelitis ('Acute Perivascular Myelinoclasis')", THE MEDICAL JOURNAL OF AUSTRALIA, Volume II, Number I, July 7, 1945, page 15.
(20) E. H. Oppenheimer: "Congenital Chickenpox with Disseminated Visceral Lesions", *Bulletin of the Johns Hopkins Hospital*, Volume LXXIV, Number 4, April, 1944, page 240.
(21) J. W. Dawson: "The Histology of Disseminated Sclerosis", *Transactions of the Royal Society of Edinburgh*, Volume L, 1916, page 517.
(22) A. Ferraro and I. H. Scheffer: "Encephalitis and Encephalomyelitis in Measles. A Pathologic Report of Six Cases", *Archives of Neurology and Psychiatry*, Volume XXV, 1931, page 748.
(23) F. Wohlwill: *"Über Encephalomyelitis bei Masern"*, *Zeitschrift für die gesamte Neurologie und Psychiatrie*, Volume CXII, 1928, page 20.
(24) E. W. Hurst: "A Review of Some Recent Observations on Demyelination", *Brain*, Volume LXVII, Part 2, 1944, page 103.
(25) F. Kennedy: "Allergic Manifestations in the Nervous System", *New York State Journal of Medicine*, Volume XXXVI, April 1, 1936, page 469.
(26) G. A. Jervis: "Forssman's 'Carotid Syndrome'. A Contribution to the Study of Anaphylactic Changes in the Nervous System from the Standpoint of Pathology", *Archives of Pathology*, Volume XXXV, 1943, page 560.
(27) E. W. Hurst: "Myxoma and the Shope Fibroma. 1. The Histology of Myxoma", *The British Journal of Experimental Pathology*, Volume XVIII, 1937, page 1.
(28) C. Swan: "The Route of Transmission of the Virus of Infectious Myxomatosis of Rabbits to the Central Nervous System", *The Australian Journal of Experimental Biology and Medical Science*, Volume XIX, 1941, page 113.
(29) B. T. Cooke, E. W. Hurst and C. Swan: "Routes of Entry into the Nervous System of Viruses Introduced into the Blood-stream. Experiments with the Viruses of Pseudorabies, Herpes and Infectious Myxomatosis", *The Australian Journal of Experimental Biology and Medical Science*, Volume XX, 1942, page 129.
(30) C. Swan: "A Case of Human Encephalitis with Type 'A' Intranuclear Inclusion Bodies", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, May 15, 1943, page 437.
(31) J. P. Horan, G. A. W. Johnston, J. H. Halliday, J. O'Brien and E. W. Hurst: "A Distinctive Type of Encephalomyelitis Occurring Among Troops in the Northern Territory of Australia: A Discussion of Two Fatal Cases", *Brain*, Volume LXVII, Part 2, 1944, page 93.

Legends to Illustrations.

FIGURE I.—Caudate nucleus. Perivascular (extraadventitial) and diffuse softening. Celloidin section (Weil-Weigert method for myelin, ×60).

FIGURE II.—Putamen. Intense diffuse infiltration, moderate perivascular and extraadventitial infiltration. Early stage of softening. Celloidin section (hæmatoxylin and Van Gieson's stain, ×120).

FIGURE III.—Putamen. Control for comparison with Figure II. (From a case of idiopathic acute disseminated encephalomyelitis[19] in a boy, aged seven years, in which the putamen was normal.) Celloidin section (hæmatoxylin and Van Gieson's stain, ×120).

FIGURE IV.—Caudate nucleus. Diffuse, perivascular and extraadventitial infiltration. Celloidin section (hæmatoxylin and eosin stain, x 120).

FIGURE V.—Putamen. Extraadventitial infiltration of a vessel. Disintegration of surrounding brain substance has led to a "spongy" appearance. Paraffin section (hæmatoxylin and eosin stain, x 290).

FIGURE VI.—*Fasciculus occipito-frontalis superior.* Perivascular (extraadventitial) demyelination. Celloidin section (Weil-Weigert method for myelin, x 60).

CONGENITAL STRICTURE OF THE ŒSOPHAGUS.

By RICHARD FLYNN,
Sydney.

Clinical Record.[1]

H.S., a boy, aged ten years, sought medical aid because he had had dysphagia since birth. He had experienced as much difficulty in swallowing fluids as he had in swallowing solid food, and the difficulty was increasing. He had found that after filling his mouth and pharynx with food he could force it down by pressing on his supraclavicular regions. He stated that at times a "lump in his throat" was palpable about the level of the cricord cartilage. Frequently he regurgitated food which he could not swallow. He had suffered from whooping cough and pneumonia when he was aged five years.

On examination, the patient was a thin, pale, ill-nourished boy with palpable glands in the axillæ and groins. On March 26, 1942, a skiagram (Figure I) taken after a barium bolus revealed almost complete stenosis of the œsophagus at the level of the aortic arch, with extreme œsophageal dilatation proximal to that level. The appearance was that of a congenital stricture causing considerable obstruction. The œsophagus distal to the aortic arch was not visualized, so that the possibility of a large diverticulum which became filled first and completely compressed the œsophagus could not be excluded.

A blood examination gave the following information. The hæmoglobin value was 71%, the erythrocytes numbered 5,380,000 per cubic millimetre, and the colour index was 0·65. The leucocytes numbered 7,000 per cubic millimetre, 60% being neutrophile cells, 3% eosinophile cells, 29% lymphocytes and 8% monocytes; no basophile cells were seen, and no abnormality was detected in the neutrophile cells. Examination of a blood film showed that the red cells varied slightly in size. An occasional small form was seen, and some cells were mildly hypochromic. No nucleated stippled or polychromasic forms were seen. The Wassermann test failed to produce a reaction. No abnormality was detected in the platelets.

On March 28 œsophagoscopy was performed under general anæsthesia, with the following findings. A tiny, pin-point orifice was seen at about the level of the aortic arch, but dilators were passed without effort. There was firm resistance to bougies. The diagnosis of congenital stricture was made. A further skiagram showed that there was still delay to the passage of a barium bolus, but the appearance was practically unchanged since the previous examination.

At this stage I was asked to examine the patient with a view to establishing a gastrostomy; but I felt that his ability to swallow might be improved by the passage of Plummer's bougies over a previously swallowed silk thread after the method of Russell (Figure I). Accordingly, on March 29, he was reassured and given a silk thread to swallow, and twenty-four hours later bougies were passed easily. Immediately after the passage of the bougies the patient was able to drink a large glass of fluid without difficulty. His weight at this time was three stone nine pounds. A few days later the stricture was again dilated, and a skiagram was taken with the bougie in position (Figure II), and later a thin barium bolus was given (Figure III). This passed through the stricture without gross obstruction, although previously a similar mixture was completely obstructed. The ordinary barium bolus was still obstructed. Dilatation was then carried out over a silk thread at intervals of one week. On April 10, 1942, his weight was three stone twelve and a half pounds, and Dr. A. Oxenham reported after a fluoroscopic examination that the patient could now swallow a barium bolus, there being only slight delay to its downward progress at the level of the stricture, while the dilatation proximal to the lesion was not so pronounced as at the previous examination (Figure IV). After further dilatation he was discharged from hospital, with the request to report again in three months' time. He returned then and on subsequent occasions, fourteen in all, during the following years for further dilatation.

Early in 1945 it was evident that though the dilatations kept him going, they were not going to cure him. At this time I had some infants with tracheo-œsophageal fistula under my care, and I felt that this boy's condition resembled that of a child who had escaped the fistula, but had developed a stricture at the site of juncture of Keith's paratracheal and retrotracheal parts of the œsophagus. The relation of the constricted area to the bifurcation of the trachea is well seen in Figure V. So, after discussion and viewing his X-ray films with Professor H. R. Dew, I exposed the patient's œsophagus on April 30, 1945, through an extra-pleural right-sided approach, with the intention of doing something in the nature of a plastic operation similar to a Finney's pyloroplasty on the constricted area.

A dilator was passed over a previously swallowed silk thread to serve as a guide to the œsophagus, and to my surprise I exposed a vein running across in front of the œsophagus, and about two inches distal I found another similar aberrant vein. These veins probably represent aberrant segmental veins of the azygos system. I ligated both of them between silk ligatures and divided them. The œsophageal wall between these two veins was much thicker than the wall proximal and distal to the veins. Because I thought that this might be due to inflammatory thickening, I abandoned my intention of dividing the œsophageal wall. I was also embarrassed because the intra-œsophageal silk thread snapped. (At this point I would suggest that the presence of an ear, nose and throat colleague with an œsophagoscope would be invaluable to the patient and of great assistance to the surgeon in all such cases.) The patient stood the operation very well.

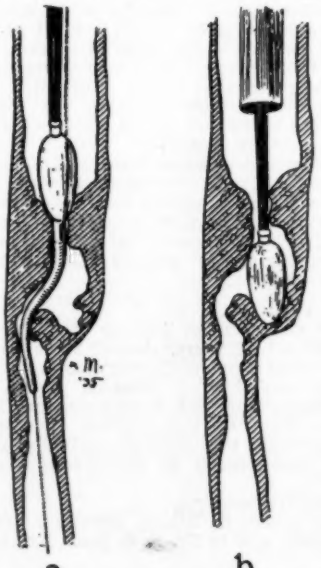

FIGURE Va.

(After Moersch.) (a) Method of introducing a dilator over guiding thread; (b) same case, illustrating the hazard of œsophagoscope without guiding thread.

Post-operative X-ray films showed that there was a large collection of fluid in the chest, which I thought was extrapleural. It was aspirated, and the child was given Wolff's bottles to increase his respiratory expansion. On May 8 he was again radiologically examined (Figure VI), and the following report was received.

There appears to be some encysted fluid in the middle zone of the right lung field, posteriorly. The ingested meal passes down the œsophagus, but the barium bolus is held up at the same level as on the previous occasion. The dilatation of the œsophagus proximal to the delay is not as pronounced.

[1] The patient was shown at a clinical meeting of the New South Wales Branch of the British Medical Association at Lewisham Hospital.

ILLUSTRATIONS TO THE ARTICLE BY DR. RICHARD FLYNN.

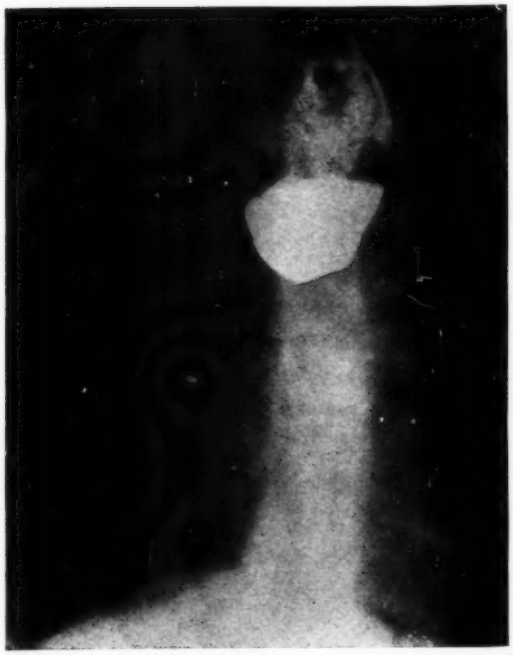

FIGURE I.

FIGURE II.

FIGURE III.

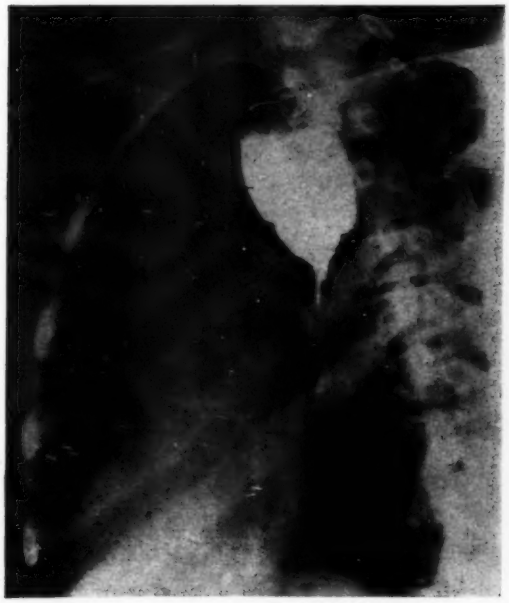

FIGURE IV.

ILLUSTRATIONS TO THE ARTICLE BY DR. RICHARD FLYNN.

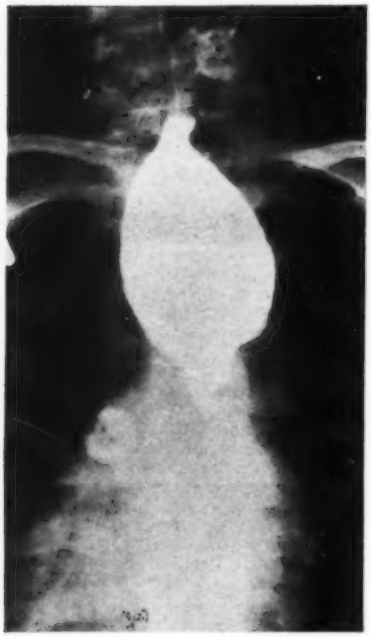

FIGURE IVA.

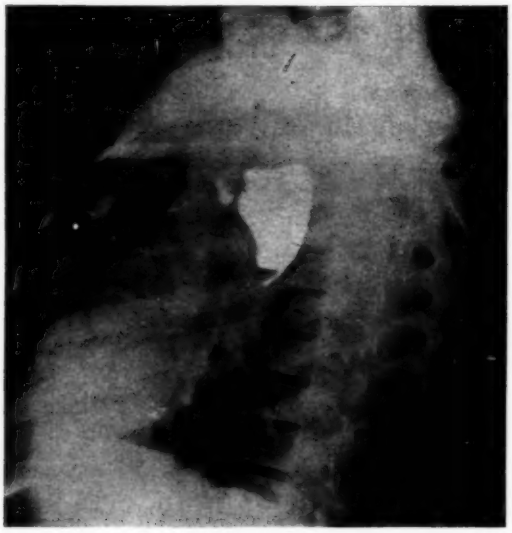

FIGURE V.
Note the relation of the stricture to the tracheal bifurcation.

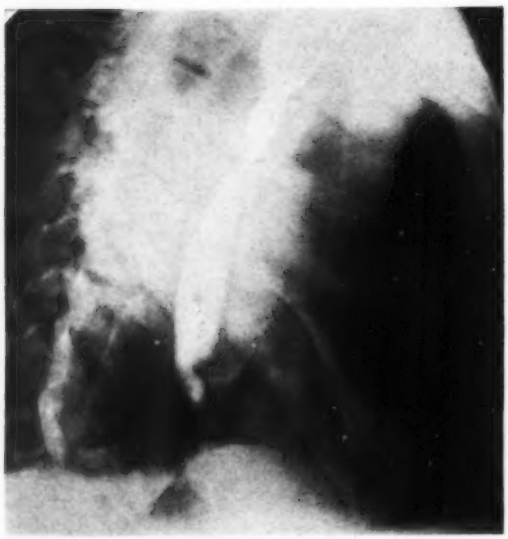

FIGURE VI.
Note the relation of the stricture to the division of the trachea into bronchi.

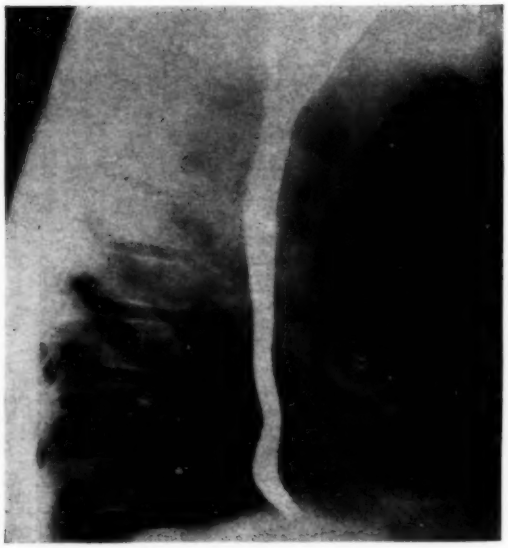

FIGURE VII.

The patient returned for a "check up" and œsophageal dilatation on July 23. Some tissue was found in the dilator, microscopic examination of sections of which revealed inflammatory changes; at the edge of the tissue a small collection of epithelial cells was present, the exact character of which it was difficult to distinguish. A further fluoroscopic examination was made on July 24, the report being as follows:

> The barium meal now passes very quickly down the œsophagus, and there is little, if any, delay at the site of the stricture, but the barium bolus is held up at this level, but the delay is not nearly as pronounced as on any of the previous examinations.

The patient was then examined by Dr. Harrison, who on August 1 reported that an œsophagoscopic examination under ether anæsthesia (intratracheal method) had revealed, approximately two inches from the upper sphincter, a crescentic, rather thick band arching over the anterior half of the œsophagus and partially obstructing it; at the right posterior lateral angle a small, white, firm area was noticed. The œsophagoscope was pushed through the obstruction and entered a zone of narrowing of the œsophagus for approximately two inches. In this area the mucous membrane appeared scarred and somewhat atrophied. At the further limit of this zone, redundant folds of normal-looking mucous membrane bulged into the œsophageal lumen. Œsophagoscopy was repeated on August 9, again under ether anæsthesia (intratracheal method). The crescentic band previously noticed was not nearly so pronounced, but otherwise the appearances were much as before. A loose piece of mucous membrane was taken for examination from the anterior aspect of the upper portion of the obstructed area. A further skiagram (Figure VII) taken on August 24 shows more improvement, and is in considerable contrast to those taken before operation (Figures IV and V).

Comment.

This case is reported because of obstruction to the swallowing of food caused by the presence of two aberrant azygos veins crossing in front of the œsophagus. It is interesting to conjecture whether the scarring which Dr. Harrison saw was due to the remains of a congenital web, or whether it represents a scarring produced by repeated trauma where the tight aberrant azygos vein crossed the œsophagus—that is, by solid food or more probably by the passage of dilators. This might readily produce œdema, fibrosis or possibly ulceration. It is important to note that the posterior wall of the œsophagus at the site of the stricture appeared normal. Emphasis has been laid on the relation of the site of the veins to the bifurcation of the trachea, and this makes one question whether there is any relation between the occurrence of tracheo-œsophageal fistula and maldevelopment in the azygos system of veins.

As to the future, I intend to keep the child under observation and dilate his œsophagus by the Plummer method at regular intervals for some years, at least until there is no relapse. On reviewing and reconsidering the skiagrams taken over the years, particularly that reproduced in Figure IV, I feel that if a similar case was met with, operative interference might be undertaken earlier.

Acknowledgements.

It is a pleasure to acknowledge my indebtedness to Professor H. R. Dew for his sharing with me the responsibility of advising operation to the child's parents, and to Dr. H. H. Harrison, Dr. H. J. Daly and Dr. A. Oxenham for their help in the treatment of the child.

Reviews.

THE SICK CHILD.

WITH "Principles of Pediatrics and Pediatric Nursing", Miss Knox has produced a most comprehensive and ambitious book[1] dealing with such diverse topics as "Early Pediatrics in Europe", "Children's Literature", "The Feeding of Infants" and "Tuberculosis in Children". The purely nursing sections of the book are excellently done. In a long final chapter on nursing procedures and technique no detail is too small to have been overlooked. There are fine sections on the general care and handling of sick children, and the psychological approach to such matters as "Emotional Problems", "The Retarded and Asocial Child" and "Habit Formation" is exactly right. Even the remarks on "Play", although no doubt commonplace to the kindergartener, will be of immense value to the ordinary children's nurse. There are some perfectly delightful full-page photographic studies of babies and children interspersed with the text.

But it seems to us that Miss Knox has been a little too ambitious. The latter half of her book deals with diseases and disorders of childhood, classified under systems, but no nurse needs descriptions of such rarities as *sclerema neonatorum*, amaurotic family idiocy, Buhl's disease and the like, or a six-page account of the disordered physiology of heart disease. On the other hand the material is too scrappy and inaccurate to interest medical students. But for the author's determination to put everything in and her attempt to reach doctors as well as nurses, this would have been the best book on pædiatric nursing yet published. Reduction to about 350 pages by cutting a lot of dull charts, much irrelevant medical matter and scores of unnecessary references would make it so.

CHEST EXAMINATION.

A SECOND edition has already appeared of R. R. Trail's handbook on chest examination and the correlation of physical and X-ray findings in diseases of the lung, which was noted in this journal on May 13, 1944.[1] There have been some enlargement and rearrangement of the contents and the number of illustrations has been increased; but the index is still very inadequate. It is an original and stimulating little book, which contains a great deal of useful information for its small size. As we remarked previously after some criticism (which we need not modify) of the literary style and of some of the applied anatomy and physiology, it is to be recommended ungrudgingly to physicians and radiologists and may well enjoy a perennial popularity.

OBSTETRIC MANAGEMENT AND NURSING.

"OBSTETRIC MANAGEMENT AND NURSING" is an extremely good and well-written textbook containing excellent illustrations, useful diagrams and many helpful photographs.[2] In particular the photographs illustrating the care of the breasts, use of the breast pump and post-natal exercises could not be better, and, from a nurse's point of view, the definitions at the commencement of chapters and the summaries and questions are also of great use.

There are several criticisms of this volume, however, which should be noted. For example: "In delivery of the baby, the fingers are placed in the rectum and vagina." This is definitely not advised and is not carried out in Australia. Again, the frequency with which episiotomy is carried out by American obstetricians is not considered good obstetrics by our standards. Episiotomy is useful and necessary in many cases, particularly in primiparous breech deliveries and in occipito-posterior positions when the head is on the perineum; but it should not be carried out as a matter of routine, because healing is often delayed and keloid formation may occur with resultant dyspareunia.

Ice bags are not used in mastitis in many cases in Australia.

It is to be deplored that "Pituitrin" is recommended to be given before conclusion of the third stage of labour. As

[1] "Principles of Pediatrics and Pediatric Nursing", by Cecilia M. Knox, B.S., R.N.; 1945. Sydney: Angus and Robertson Limited. Philadelphia: F. A. Davis Company. 8½" × 5½", pp. 537, with illustrations, some of which are in colour. Price: 26s.

[1] "Chest Examination: The Correlation of Physical and X-Ray Findings in Diseases of the Lung", by Richard R. Trail, M.C., M.A., M.D. (Aberdeen), F.R.C.P. (London), with a Foreword by Sir Walter L. Langdon-Brown, M.A., M.D., F.R.C.P., D.Sc., LL.D.; Second Edition; 1945. London: J. and A. Churchill Limited. 8½" × 5½", pp. 135, with 94 illustrations. Price: 12s. 6d.

[2] "Obstetric Management and Nursing", by Henry L. Woodward, M.D., and Bernice Gardner, R.N., with a section on home deliveries by William P. Gillespie, M.D., and also with a section on diseases of the newly born by Harold F. Downing, M.D.; Second Edition; 1944. Philadelphia: F. A. Davis Company. 8½" × 5½", pp. 772, with many illustrations. Price: 28s.

a rule, "Pituitrin" should never be given before expulsion of the placenta. The two exceptions are in multiple pregnancy after delivery of the first baby and after rupture of the second amniotic sac and in cases in which no pains result in one hour from rupture of membranes.

In summary it may be stated that this book is extremely well written; every detail has been recorded, with liberal use of instructive photographs and many small practical points useful to nurses. The numerous and excellent diagrams and X-ray pictures make it a valuable book which should have a strong appeal to nurses, medical students and practitioners.

PRINCIPLES OF PHYSIOLOGY.

SINCE Starling's death in 1927 the periodical revision of his "Principles of Human Physiology" has been in the capable hands of his successor to the chair of physiology at University College, London.[1] Although the general form of this standard work has remained much the same since its first appearance in 1912, its content has changed so materially that Professor Lovatt Evans is now very properly regarded as its author.

In the latest (ninth) edition, apart from numerous minor alterations and additions, the main changes are the introduction of historical notes to the principal sections, and the complete recasting of the chapter on the heat balance of the body. Much of the recent work on this subject is now included, especially that dealing with the effects of the temperature and humidity of the environment, as, for example, Lee's work in Queensland. The statement in an early paragraph of this chapter that the heat loss from the body approximately equals that leaving the skin needs revision. Even in man loss from the respiratory surfaces is of importance.

A book of over a thousand pages is rather formidable for use as a text by the average medical student, but this one should be constantly at his hand for more intensive study as a work of reference from the smaller text that he may be using. For the more serious student and for the graduate it is, of course, essential.

When this book first appeared biochemistry was taught in most medical schools as a part of physiology. It was thought necessary to include in any textbook of physiology what biochemical information the student required. This tendency is still to be seen in the latest edition of this book. About a third of the book is devoted to the discussion of biochemical topics. This perhaps is in part a survival and in part a reflection of the biochemical trend of many of the author's own investigations. The increasing dependence of physiology on biochemical methods and information must be fully recognized, but there are now many excellent textbooks of biochemistry which deal better with what the medical student should know of this subject. A textbook of the dimensions of this work might profitably be relieved of a good deal of this matter. As the book already contains an excellent selection of references to original sources, a few references to biochemical texts suitable for concurrent reading might well be included.

The production of the book is of pre-war standard. It shows little trace of the difficulties which must have attended its preparation during the closing stages of the war. As in the previous edition, the chapters on the special senses have been revised by Professor H. Hartridge.

A DISSECTING MANUAL.

BOILEAU GRANT AND CATES have produced a second edition of their small dissecting manual.[2] Numerous changes have been made in this edition. The handbook was originally written for use in conjunction with Boileau Grant's "Method of Anatomy" even to the extent of leaving the description of the dissection of certain regions to this latter book. Now this handbook has been left to exist of its own right and all references to the larger work have been removed; various sections have been added, so that the dissections now cover the whole body.

The book is a straightforward guide to the successive steps of the routine dissection of the human body. The illustrations are practically confined to the skin incisions. Although the book is clearly written and well arranged, we consider that the student will need to make extensive use of his standard textbooks and atlases if he is to find many of the structures that he is supposed to find. This remark applies particularly to the student dissecting for the first time. The inclusion of good illustrations would largely overcome this difficulty.

The book is well printed, and in format is a convenient size to handle in the dissecting room. An adequate index is also provided.

[1] "Principles of Human Physiology" (originally "Starling's Principles of Human Physiology"), by C. Lovatt Evans, D.Sc., F.R.C.P., F.R.S., LL.D. (Birmingham); with section on the special senses by H. Hartridge, M.A., M.D., Sc.D., F.R.S.; Ninth Edition; 1945. London: J. and A. Churchill Limited. 9¼" × 6", pp. 1165, with many illustrations. Price: 36s.

[2] "A Handbook for Dissectors", by J. C. Boileau Grant, Professor of Anatomy, University of Toronto, and H. A. Cates, Associate Professor of Anatomy, University of Toronto. Second Edition; 1945. Baltimore: Williams and Wilkins Company. 7½" × 5", pp. 390, with nine illustrations.

GYNÆCOLOGICAL DIAGNOSIS AND TREATMENT.

A SECOND edition of "The Symptomatic Diagnosis and Treatment of Gynæcological Disorders", by Margaret Moore White, appears only two years after the first edition.[1] Some minor alterations and additions have been made and recent advances in treatment are included, such as the use of penicillin in gonorrhœa. Common gynæcological symptoms, their causation and treatment appropriate to the cause are discussed clearly and concisely. This method of approach makes the book valuable to the general practitioner, for whom indeed it is specially intended, to enable him to apply the best methods of treatment for minor gynæcological disorders and to recognize the conditions which should be referred to a specialist.

There are some omissions. For example, no warning is given of the likelihood of delayed menstruation when œstrogens are used; the correct time for the performance of an insufflation test or a hysterogram is not indicated, and in the discussion on treatment of trichomonas vaginitis by vaginal insufflation of a powder, pregnancy is not mentioned as an absolute contraindication on account of the danger of air embolism.

The chapter on sterility is excellent; an account of the technique of artificial insemination has been added in this edition. At the end of each chapter a few lines emphasize the commonest errors in diagnosis and treatment.

The book may be recommended as most useful for the general practitioner.

Notes on Books, Current Journals and New Appliances.

STORIES OF THE PACIFIC.

FRANK CLUNE is the sort of Australian who is met among the Sydney *Bulletin's* contributors—intensely interested in his own country and its neighbours, articulate and not parochial.

In his "Pacific Parade", Clune has put into a book twelve little stories, unconnected except that each concerns some place in, or bordering, the Pacific Ocean.[2] They range from a tale of Botany Bay to a description of a ritual dance in a temple in French Indo-China not long before the war.

Clune writes, not as a globe-trotter, nor yet as a smart young journalist who has spent a few months in a place trying to find "inner forces" or "hidden meanings", but as a red-blooded man with more insight and intelligence than is usually found in such a person.

He knows the Pacific lands and is interested in them, and has added what he calls "a drop in the ocean of Pacific literature", already written (some by him) and still to be written.

The book is easy to read and would make a good introductory lecture in that course of Pacific affairs which it now behoves all Australians to tackle.

[1] "The Symptomatic Diagnosis and Treatment of Gynæcological Disorders", by Margaret Moore White, M.D. (London), F.R.C.S. (England), M.R.C.O.G., with a foreword by F. J. Browne, M.D. (Aberdeen), D.Sc., F.R.C.S. (Edinburgh), F.R.C.O.G.; Second Edition; 1946. London: H. K. Lewis and Company Limited. 8¼" × 5¼", pp. 256, with 108 illustrations. Price: 16s. net.

[2] "Pacific Parade", by Frank Clune; 1945. Melbourne: The Hawthorn Press. Sydney: Angus and Robertson Limited. 8" × 5", pp. 132. Price: 6s.

The Medical Journal of Australia

SATURDAY, MAY 18, 1946.

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Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

EYES.

THE eye is an avenue to adventure. It is a dormer to the mind within—a sentinel to the wise, a temptation to the foolish; for all the world comes sharply into focus through the lens and all the traffic of mankind plays upon the retinal screen. The vitality of the face rests upon the eyes and is intensified by their varied lights. The eyes range the complete scale of emotional enharmonics, from the muted minor mode of despair to the confident major concord of joy. They speak all languages. They avow and dissemble with equal facility. In their depths may lie the cipher of seduction, and secret messengers often play within a glance. Rude and intemperate discourse may flash from eyes that bind the tongue to silence; and murder, traitorously conceived, may hover in the declaration of a look.

"A gray eye is a sly eye, and roguish is a brown one", sang an Oriental poet, and poets the world over have praised and described the particular colour of their mistresses' eyes. Blue is the most popular colour; though Shakespeare and Byron seem to have had a partiality for black or very dark eyes. Longfellow liked the "flash of keen, black eyes"; while Somerville preferred them large and sloeblack, ready to "melt in soft blandishments". Swinburne liked green eyes, and Francis Thompson favoured grey. Matthew Arnold could not quite make up his mind, and compromised with "Eyes too expressive to be blue, too lovely to be gray". Pink eyes are pathological and only seen in albinos; although Shakespeare's Bacchus had "pink eyne". Robert Louis Stevenson most admired his wife's eyes which he described as of "gold and bramble-dew". Some individuals have a different colour in each eye, like the Roman Emperor Anastasius I, who had one black and one blue eye. And though acute inflammation may redden the loveliest eye, Pyrrhus is said to have had eyes like carbuncles.

To the evangelist, the light of the body is in the eye; and if the eye is evil the whole body is filled with darkness. The clinician, however, is more worldly; and the eye to him is an organ of special sense, subject to the same pathological changes as other bodily tissues. He knows the elements of optics, and, if not alien to gallantry, he may understand the shaded message of an eloquent eye. He may see in the pupil more peril than a naked sword, or glimpse death's courier behind the curtain of the iris. His diagnostic mind is intrigued by a twinkle, and a tear may bring him fresh discernment. His practised hand is as ready to extract the mote as to cast out the beam. Inflammation interests him and a *gutta pro oculis* is soon exhibited and the eye-bath procured. Fever-bright eyes may capture his passing attention in the sick ward. He may notice the bulging exophthalmos of the strumous woman in the clinic or comment upon the squint of a child brought to his care. He may remember the eye changes in oxycephaly and *leontiasis ossea* if he ever sees such cases, and if he resides in America he may be familiar with the ophthalmic complications of tularæmia. The eye in affliction may be a signal to the neurologist who goes quickly to the scent of an ocular palsy or a unilateral ptosis. To him there is meaning in a hippus; and unequal pupils may presage the impending dementia of the paretic. He marks the "oculogyric crisis" of the post-encephalic and the nystagmus of the multiple sclerotic. For the eye may be as changeable as a weathercock, but its motions are meaningful and often bodeful.

Mythology is sometimes mimicked by the monstrosities which medical science cherishes in its pathological museums. Cyclops, for instance, could make no thunder for the gods when, as reported by Vallentini, being born with a single eye in his forehead, he lived for only seventy-three hours. Nor could a similar individual, reported by Blok as having survived only six hours. Cases are recorded in the literature in which both eyes were absent; other cases in which there was a single orbit containing two eyes. The *American Medical Review* reports a child with eyes on the top of its head, as if capricious Nature was anticipating air-raids. Multiple pupils and double lenses are on record. But the inventive fancies of the ancient myth-makers have never been completely surmounted by the most prodigious mistakes of reproduction. Though the "four-eyed man of Cricklade" could revolve each eye separately in its orbit, no monstrosity yet born has rivalled Argus, the herdsman, who had eyes all over his body, nor the seven-eyed lamb depicted in the Book of Revelations; nor has pathology any prodigy similar to the Graiæ, those repulsive sisters who owned between them but one eye and a single tooth.

The eye was the symbol of Osiris, the saviour of the world, and Horus, his son, whose eye was swallowed by Set to mark the night from the day. And other gods in other hierarchies have elevated the eye to the status of a symbol; but Siva, the hermaphrodite god, went further by placing an auxiliary eye upon his forehead to symbolize the two creative forces. In a subsequent epoch the eyes of Jehovah were in every place, and looked upon them that feared Him. The eye of Heaven neither slumbered nor slept. So when Saul was travelling in the desert he was smitten with temporary blindness, his eyes having been dazzled by the light of God. And Tobit, having carelessly allowed sparrow's dung to fall into his eyes, became blind and went to the physicians who helped him not. But his son rubbed the gall of a fish upon his

sightless eyes, and he saw again and rejoiced. Other cures for blindness by the application of fasting spittle take us back to folk-lore and fable where science refuses to dwell; while many of the most modern cures depend upon the surgical miracle of the "corneal transplant".

Sometimes, as the result of violence or misadventure, the eye is dislocated from its socket; and cases have been reported of extrusion of the eyeball by excessive and violent coughing or by vomiting. The eye may be the seat of unconscious emotional conflict for, as the organ of sight, it may have glimpsed tabooed objects. Unconscious guilt at having viewed the forbidden may occasion hysterical blindness or psychotic mutilation of the organ. The Biblical injunction "If thine eye offend thee, pluck it out" is seldom obeyed in the letter by contemporary Christians; but there is a record of a French woman who, while suckling a child, came upon this passage in the scriptures and, inflamed with a sudden necessity for literal obedience, enucleated her eye with a meat-hook. Tradition parallels this case with the conduct of Saint Triduana who, when her eyes were admired by a Pictish chief, plucked them out and presented them to him nicely impaled upon a skewer. No sanctity can be attested, however, in the case of the Dublin medical student who extirpated his eyes and threw them on the grass because he was mad; nor may any devout vindication be found for the intoxicated woman in the same city who tore out her eyes with her nails.

Blinding was a common punishment which persisted until about the fourteenth century. Sometimes the eyes were gouged out with the fingers; at other times they were burnt out by hot irons. Jehovah who intimidated the recalcitrant Israelites threatened to smite them with madness and blindness so that they would grope at noonday "as the blind gropeth in darkness". The Babylonians used blinding in the case of troublemakers whom they wished to incapacitate and restrain from causing further harm. They put out the eyes of the Israelite king Zedekiah and bound him in fetters. The Philistines thus mutilated Samson and kept him "Eyeless in Gaza at the mill with slaves". And the young duke Arthur, in Shakespeare's play, saved his eyes from the hot iron's searing, by the poetry of his pleading with Hubert. With murderous cruelty in a later play Gloucester's eyes were gouged out by Cornwall, who swore that "Upon these eyes of thine I'll set my foot". And when the deed was done, said sneeringly: "Out, vile jelly! Where is thy lustre now?"

Terrible in the past was the power of the evil eye which could wither and slay at a glance. Children had to be especially protected from it. Food and drink were vulnerable. Crops could be ruined, trees and shrubs made to lose their leaves, and cow's milk turned to blood by its influence. Many quaint contemporary customs persist in a modified form as examples of its effects in times when magic supplied the only explanation of natural happenings, when amulets were worn by rich and poor, and rue, onions and garlic were among the most potent protectives. At one time the Chinese and Japanese placed mirrors on the roofs of their houses to ward off the evil, and many superstitious people once nailed up human or animal phalli on the doors of their dwellings where now the emblematic horse-shoe is sometimes displayed. Cripples and eccentrics were often thought to possess an evil eye, especially if they had a "cast" or some pupillary abnormality. Pius IX was said to have had a malefic eye; so, apparently—if one may jump from the living to the legendary—had Wotan. A fabulous monster which could kill with a look, but died at the sound of a cock-crow, was the cockatrice whose evil eye was deadly to man and to all animals except the weasel which, if wounded in combat, had immediate recourse to rue, the only plant the cockatrice could not wither. The basilisk with its death-darting eyes was a similar prodigy of ancient awe and superstition; and the petrifying glance at the Gorgon seems also to belong to the same venerable symbolism.

The evil eye no longer casts its baleful look. Modern man is plagued with other mischief. When he surveys the scene of his earthly estate it is with mingled feelings of care and contentment, trailing his eyes in sorrow and raising them in moments of rapture and inspiration—goggling at the curious and grinning through the horse-collar of popular jest. Science has extended his vision so that he sees more than his ancestors, but it is doubtful whether his mind is thereby more enchanted. The eye of reason is still bespectacled with doubt; and the purblind eye of prejudice continues to mislead. The eye's falsehood may disturb the heart's judgement and confute the logic of the other senses. For all the eyes behold is evanescent and memory cannot long contain its teeming imagery which becomes blurred in the profusion and soiled in the commerce of the commonplace. Then the day comes when the mind's mirror grows tarnished and perception wanes as the days run together. The light that was sweet becomes tedious and misty, and in the shadow lies the grave, and the final consummation is in darkness, when the eye, which for a little while compassed wonder, is closed and sightless forever.

Current Comment.

TRANSIENT DISTURBANCES FOLLOWING HEAD WOUNDS.

THERE is not necessarily any close parallel between head injuries due to accident and those due to gunshot wounds. A high-velocity missile on striking the skull exerts a disruptive effect over a small area, and even when the missile glances away without entering the skull a shower of fragments may penetrate the brain for a little distance. With these high-velocity missiles focal injury may dominate the clinical picture, even though consciousness may be little impaired. A small scalp injury may thus be associated with a focal cerebral injury which may leave permanent residual signs. In complete contrast is the familiar sequel of sudden complete loss of consciousness after a blow on the head, with slow recovery and without any focal symptoms.

W. Ritchie Russell has studied the transient disturbances following gunshot wounds of the head, with particular emphasis on the physiological principles involved.[1] These disturbances may be motor or sensory or both. Russell comments on the cortico-spinal shock which may occur, causing immediate paralysis and loss of tendon reflexes in a limb. It is interesting that the upper limb is more susceptible than the lower, owing no doubt to the greater intricacy of the cortical influence over the lower motor neurones. The motor cortex is in general more susceptible to shock of this kind than the sensory cortex, but it is comforting that motor function can make a remarkable recovery, after a latent period of one or two days in the case of the lower limb, and ten days or more in the case

[1] *Brain*, Volume LXVIII, Part II, 1945.

of the upper limb. Of course, permanent disability may result, even if no deep obvious wound of the brain has occurred, and this is more likely when the wound is in the region of the Rolandic area. Sensory disturbances from wounds of the type under consideration are of particular interest. Russell points out that modern physiological work indicates that there is a close anatomical and physiological connexion between the posterior ventral thalamic nucleus and the post-central cortex, and that this reciprocal thalamo-cortical system of connexions is a common functional unit. Injury in the Rolandic region may produce quite a profound transient loss of all forms of sensation over the opposite side of the body, which often tends to be confined to one limb, while the adjacent limb area may be spared. Recovery from these losses of cutaneous sensation may be slow and is often incomplete, and areas of permanent loss may often be segmental in type, suggesting that the causative lesion is at cortical level. Russell has found that in cases in which any profound impairment of all forms of sensation persist as a permanent disability, it is usually due to damage from a wound near the precentral area. Study of the distribution of this permanent loss has confirmed its cortical origin. A feature of some importance in injuries of the type under consideration is the occurrence of perverted sensation. Increased sensitiveness to cutaneous stimulation and to pain perception may occur as a sequel and also disordered sensation. The over-reaction to pain may be of the type described as thalamic. Russell's experience is that spontaneous pain associated with cortical trauma is not so severe as that found after damage at or below the thalamic level, though paræsthesia may be troublesome. It would seem that sensory over-stimulation may arise at any level in the nervous system.

Russell, in conclusion, emphasizes the value of clinical study in these cases, and the need for coordinating the results with the work of the anatomist and the physiologist. The importance of careful study was also emphasized by R. A. Money and T. Y. Nelson in an article on battle wounds of the head.[1] They pointed out that signs of unilateral focal damage of the brain do not call for extensive operations unless signs of compression are present, but they should be serially recorded by observers trained in neurology. They further gave the warning that an apparently minor wound of the head may be more serious than at first appears, and should receive all the care and attention it deserves.

TOXIC FACTORS IN EXPERIMENTAL SHOCK.

IT is still very difficult to reconcile all the phenomena associated with shock in one simple hypothesis. But amidst all the confusion there is still good reason for believing that chemical factors play an important part. For that matter they are of great importance in the ultimate mechanisms of all bodily functions. A series of studies has been published by a group of workers from Boston, including I. T. Nathanson, A. L. Nutt, A. Pope, J. C. Aub, P. C. Zamecnik, D. M. Tibbetts, A. M. Brues, R. T. Dubos and S. S. Kety.[2] Their studies concern toxic factors in experimental shock, and they begin by evolving a method by which a modified degree of shock could be produced by trauma in an anæsthetized animal. Overwhelming shock was avoided, so as to give an opportunity for study of the early physiological reactions and possible means for their relief. The method used was to isolate the large calf muscles of a dog under anæsthesia with full aseptic precautions, and to compress them by a tourniquet for five hours, after which the tourniquet was removed. The circulation was then reestablished and the wound resutured. Arrangements were made to collect the fluid draining from the damaged muscle. Following this procedure, which involved about 1% of the body weight of the animal, shock was observed in certain cases. Study could be made of the nature of the fluid exudate, and of the results accruing from the absorption of the constituents of muscle into the circulation. Other conditions such as blood loss could be superadded to the effect of ischæmic damage. In spite of all surgical precautions the fluid draining from the muscles was heavily contaminated with bacteria in nearly every case, and this factor in the production of shock was given careful consideration. Simple muscle ligation produced shock only in about one-third of the cases, and when muscle drainage was also practised shock was not observed in any case. A rise in the blood creatine level was found to occur after the muscle tourniquet was removed; muscle so damaged is known to lose up to 70% of its creatine, and apparently this is the cause of the systemic rise. Experiments were carried out on the blood and tissue electrolytes and extracellular space determinations were made. These showed changes in the traumatized areas, but the only significant alteration in the body fluids was a terminal rise in the plasma potassium. Observations were also made on the effects of muscle damage by anoxia on the amount of vascular fluid; it was found that a local loss of fluid was a more plausible cause of shock than the action of any generalized toxin. Now it may be asked what effect the drainage fluid from the damaged muscle would have if introduced into the circulation. Extracts of crushed tissues have often been found to produce vaso-depression, hæmoconcentration and death. The authors point out that in such experiments bacteriological studies have not been made, and usually little attempt has been made to prevent bacterial contamination. In the present experiments the muscle exudate was injected either into the same dogs or into others. Only in one-quarter of the cases were any signs of shock demonstrated. This inconstancy is curious, and the authors feel that it is suggestive of an extraneous agent, rather than one derived from the cellular constituents and metabolic products of muscle exudation, for in this regard their work has not been enlightening. Such a substance might be of bacterial origin. Further study of the muscle exudate from the chemical point of view shed little light on its toxicity. Pooled exudates yielded a toxic fraction which was non-dialyzable and therefore probably protein. Two enzymes were found, but no correlation could be established between the enzymatic activity of the exudate and its toxicity. But it was found that if muscle tissue was minced and incubated with sterile plasma for five hours the plasma acquired toxic and indeed lethal properties. The explanation of this change was found in the invariable presence of bacteria in the plasma, for if it was sterilized by filtration before inoculation into an animal it was harmless. Apparently even the most rigid aseptic techniques cannot always be relied upon to exclude clostridia from biopsy specimens of normal dog's muscle, although they are not found in similar specimens of normal human muscle. Perhaps this work seems negative, inasmuch as it reveals no intrinsic cause of shock derived from muscle traumatized by anoxia. The bacterial factor has been proved to be of great potential and actual importance in experimental shock, though, of course, it can be only one facet of the subject in general. What relationship clostridial infection may bear to human wound shock cannot be stated in general terms; but that this work lays emphasis on the importance of bacterial contamination in traumatic wounds cannot be gainsaid.

OVARIAN CARCINOMA IN A FŒTUS.

STATING that he has found no record of the occurrence of carcinoma in a fœtus, E. E. Ziegler, in *Archives of Pathology* for October, 1945, reports the discovery of bilateral carcinoma in a thirty weeks fœtus. The tumour was found in a routine examination. The mother, who was healthy, had a good family history and was well twelve months after the fœtus was delivered. The tumour appeared to arise from granulosa cells, but had the morphological characteristics of dysgerminoma. This occurrence will be of interest to those who attach weight to hereditary rather than to environmental factors in the causation of cancer.

[1] *Annals of Surgery*, July, 1943.
[2] *The Journal of Clinical Investigation*, November, 1945.

Abstracts from Medical Literature.

OPHTHALMOLOGY.

Disciform Degeneration of the Macula.

HUGO LUCIC (*American Journal of Ophthalmology*, September, 1945) reports ten cases of disciform degeneration of the macula, all occurring in white sailors aged between seventeen and thirty-seven years. It came on fairly suddenly, caused considerable loss of central vision, and the ophthalmoscopic appearances suggested malignant melanoma. There is a raised pigmented patch at the macula, and the retina shows lines of tension and late hæmorrhages and some displacement of pigment. In one case a diagnosis of melanoma was made and the eye was removed. Section showed a serous exudate between the pigment epithelium and Bruch's membrane. The retina was normal, but round-celled infiltration of the choroid was present. Some organization was present in the serous exudate. The author is of the opinion that senile disciform degeneration of the macula and juvenile disciform degeneration are the same disease complicated in older people by the presence of arteriosclerosis. No definite cause was found, though most patients had focal sepsis and gave a positive reaction to tuberculin. For treatment nicotinic and ascorbic acids, multiple vitamins, choline, sodium nitrite and anti-typhoid vaccine were tried, with no definite effects. The condition seems to run its course and to subside gradually. A number of drawings of the fundi in these cases show the need for differentiation from malignant melanoma, and stress the need for the surgeon to hold his hand when melanoma is suspected.

Closure of Cataract Incisions.

IRIS PROLAPSE is the most common and worrying complication of cataract extraction. A. C. Hilding (*American Journal of Ophthalmology*, August, 1945) carried out certain experimental work to determine its causation and developed two types of operation to avoid its occurrence. Experiment proves that peripheral iridectomy was only of value if the hole in the iris was immediately beneath the point at which the wound opened when prolapse occurred. On this evidence the first technique was evolved. Two corneo-scleral sutures were inserted at the 10.30 and 1.30 o'clock positions, and after extraction three iridectomies were done at the 9.30, 12 and 2.30 o'clock positions. Any prolapse would occur between the sutures, and iridectomy was ready to deal with it in the predicted places. Satisfactory though this method may have been, it was far too mutilating and led to much adverse comment. The new technique consists of deeply grooving the limbus with a Curtis knife and inserting four corneo-scleral sutures at the 10, 11.15, 12.45 and 2 o'clock positions. These are held aside, a stab is made with a Graefe knife, and the section is completed with corneal scissors. The lens is removed in the usual way and the sutures are tied. The four sutures give strong and accurate apposition, so strong that since this method has been used hardly any prolapses have occurred. Moreover, corneal distortion with resultant high astigmatism has been rare, over 2·50 diopters in less than 15% of cases. The one drawback is the long manipulation required to insert the stitches before the main task is begun.

Blinking.

A. HALL (*The British Journal of Ophthalmology*, September, 1945) took up the study of blinking from the observation that in the chronic encephalitic its rate is much less than normal. In ordinary conversation the average person blinks 25 times per minute, the encephalitic 10. In reading the average rate is only 3·3 per minute; with the encephalitic the rate is 2·9; the blinks usually corresponding to punctuation marks, paragraphs or pages. During concentration on special print the average rate is only 1·3 per minute. Blind, even congenitally blind, people blink at the normal rate. The old view that the purpose of blinking is to keep the cornea moist seems most improbable. The rate is not affected by dryness or heat. Nor does the cornea of the chronic Parkinsonian become dry, though he blinks only once every two or three minutes. Tests carried out at the Edinburgh Zoo show that the herbivora blink on the average ten times per minute (horse twenty), whereas the carnivora average less than two (cat and lion less than one). In their native state the herbivora are the hunted; their lives depend on their alertness to danger; their peripheral vision is very sensitive and blinking accompanies each movement of the eyes as another area is scanned. The carnivora need seldom fear attack, but in stalking their prey they must fix it and keep it on the macula. And these considerations apply to man. He may be "hunted" socially, in which case he blinks fast, and, as a rule, with each blink changes the direction of his vision. Or, when he is "preying", intent on a task, he may blink very little. There remain also the conditioned reflex blinks acquired by certain types of training.

Eclipse Blindness.

DURING a total eclipse of the sun the corona radiates about as much energy as the moon. The surface of the sun at 6,000° C. radiates 160,000 times as much energy as the average surface of the earth. C. McCulloch (*American Journal of Ophthalmology*, October, 1945) points out that any ocular damage must be done by exposure of the eye to the rays of the photosphere. In routine examinations of 1,000 men he found seven who had viewed an eclipse some years previously and sustained damage to the macula. In most cases the investigation started from the story that since a certain year (when the eclipse occurred) central vision had been defective, and that visual acuity was better looking just off an object. The visual acuity was lowered in all cases and a small central scotoma was found in six of the seven. In the fundi the macula region presented characteristic features. The macula acts as a minute concave mirror, and light thrown into the eye is reflected back to form a real inverted image in the vitreous. If the macula is focused accurately this is diffuse; if now a + 2 diopter lens is put up on the Recoss disk, it is seen as a brilliant spot of light—the image of the source of light in the ophthalmoscope. This normal reflex was absent in all cases owing to damage to the fine concave structure of the macula. In addition abnormal yellow spots with or without diffuse pigmentation were noted. These must be carefully distinguished from toxic amblyopia, suppression, colloid bodies or early "hole" at the macula.

Diathermy for Glaucoma.

FOR the relief of tension it is necessary to increase drainage or diminish flow. The latter method was tried years ago by Vogt, of Zürich, who coagulated part of the ciliary body with diathermy. F. W. Stocker (*Archives of Ophthalmology*, September, 1945) has had experience of over 100 cases in which he has used cyclodiathermy. It was applied first only in desperate cases of glaucoma which had been unsuccessfully treated by several of the various surgical procedures. Its use was roundly condemned by men in high places for simple glaucoma. In the Negro, however, the beneficial results of a filtering operation are more likely to be nullified by cicatrization than in whites. It was therefore thought justifiable to treat a group of sixteen Negroes in the early stages by diathermy. A fine platinum needle 0·5 millimetre long is used with a current of about 20 milliamperes for one second or a little longer. The number of punctures made was the number of millimetres of mercury of tension *plus* 30 (for example, tension 40, number of punctures 70). The area covered is that of the *pars plana* of the ciliary body, that is, from 3·0 to 6·0 millimetres from the limbus. In every case the tension dropped and remained low. No late infection, cataract or rapid deterioration occurred. What has proved effective in the Negro may become the method of choice for the white race.

Hypotropia.

EVERY ophthalmic surgeon who operates for strabismus must have noticed that the muscle with the excessive pull is usually well nourished and strong, whereas its opponent is thin and weak. O. H. Wagman (*American Journal of Ophthalmology*, November, 1945) states that this weakness is due to paresis and that the probable date of onset of the paresis coincides with that of the acute infection which so frequently precipitates a squint. By analogy he argues that in cases of hypotropia the "down shoot" may be due not to overaction of the superior oblique muscle, but to weakness of its opponent, the inferior oblique. Also that, whereas in lateral deviations recession is often insufficient unless accompanied by advancement, so in vertical deviations advancement or "resection" of the inferior oblique muscle may be better treatment than recession of the superior. "The proof of the padding is in the seating", and the author describes first the method of Chavasse and Wheeler in which the muscle is approached through the skin of the lower lid, detached at the orbital margin, drawn out and shortened. He prefers to tackle the problem at the other end, and uses a method by which, after the external

rectus is cut, the inferior oblique is identified and traced back to its insertion just below and lateral to the macula. He then resects a portion and sutures the muscle to the stump of the insertion. This is the more useful because in some cases an esotropia as well as a hypotropia has to be corrected, and both the inferior oblique and the lateral rectus can be shortened through the same conjunctival wound.

OTO-RHINO-LARYNGOLOGY.

Fenestration of the Labyrinth.

I. SIMPSON HALL (*The Journal of Laryngology and Otology*, May, 1945) states that in fenestration of the labyrinth he uses for magnification a "Reichert" dissecting microscope giving magnifications of from about six to fourteen times, at a working distance averaging fifteen centimetres. A lighting apparatus is integral with the instrument. A flexible drive from a dental engine and various types of drills are employed. The apparatus is covered with sterilized material and the handpiece is boiled in oil and lubricated with sterile paraffin. Local anæsthesia, with the addition of "Pentothal" when needed, has been found effective. Latterly the author has preferred heavy premedication followed by light ether anæsthesia, and finds that the delay caused by increased bleeding is more than compensated for by the greater speed of working which can be achieved under general anæsthesia. The average duration of the operation is two hours. The post-aural incision has been used. The author has used the endaural approach and finds it a matter of indifference which method is used; but he advises the employment of the methods of mastoid surgery in which the operator has become trained. A flap of the skin of the postero-superior wall of the auditory canal continuous with the tympanic membrane is carefully separated and preserved for subsequently turning back to cover the fenestra when made in the external semi-circular canal. The opening is made at a place where it is judged that it will be over the ampulla of the horizontal canal, and to this end a point just anterior to a line projected upwards from the head of the stapes is selected. The depth of bone to be burred through at this point varies within wide limits. The meatal flap is finally spread over the fenestra and secured in position with paraffin packs. The incision is closed. The cavity is left undisturbed for five to seven days. In the majority of cases skin grafting of the cavity is carried out at this point, and treatment, consisting of mopping and dusting, as for any mastoid cavity, is subsequently continued. Healing takes on an average six to eight weeks, and thereafter the patient has to be seen at lengthening intervals. Symptoms of labyrinthine irritation are usual for about four days, but some patients experience more such reactions than others. There have been no cases of labyrinthitis or facial paralysis. The most troublesome complication has been infection of the cavity, and although such infection militates against success, it does not imply failure. One hundred and two operations have been carried out. The author excludes from his group for analysis of results his earliest cases, and also those of less than five months' standing. Seventy-one cases of the intermediate period remain, and of these improvement in the hearing is evident and has remained so in 54·9%. A higher percentage of good results is evident among the patients more recently operated upon. The author attributes this to more critical selection and in some measure to improved technique and increased skill. Removal of the incus since regularly practised has produced a higher percentage of good results, possibly since this permits the opening to be made larger and more anteriorly. Revision of the fenestra was undertaken three times, but was found technically very difficult, and the membranous labyrinth was in one case firmly fused to the tissues covering the fistula. The advisability of attempting revision in unsuccessful cases has still to be decided. Selection is essential for the production of good results. It is found occasionally, however, that a brilliant result is obtained in an apparently unfavourable instance. Patients with evidence of marked inner ear disease and those with evidence of middle ear disease or of sinusitis or naso-pharyngeal disease are unsuitable. Persons under thirty years do better than the elderly. Closure of the fenestra is the most important cause of failure; cartilage implants may help to avoid this. The fact that many patients come on the recommendation of others already operated upon is considered to be evidence that it must be considered worth while to submit to operation in order to obtain benefits which have been observed in others.

Effect of Aircraft Noise on Hearing.

B. H. SENTURIA (*Archives of Otolaryngology*, May, 1945) discusses the effect of aircraft noise on hearing. He states that an audiometric study was first made of 500 healthy young men, already accepted as fit to become members of aircrews. The findings were in agreement with the observations of other otological research workers, that less than half the number of supposedly normal persons tested by audiometer are found to have normal hearing throughout the tone range. Of the 500 cadet airmen tested, only 33% showed threshold curves which did not deviate more than ten decibels below the accepted zero line at any frequency from 1,024 to 11,584. Tonal dips of fifteen decibels or more in frequencies above the speech range were found in 26%, while in 21% there was progressing up the scale a high tone loss of over ten decibels. Aircraft noise was found to reach 128 decibels in open trainer types of aircraft. In better insulated enclosed bomber types the noise was reduced to about 95 decibels. In the laboratory it was confirmed that auditory fatigue could be produced with pure tones in all persons, although susceptibility varies in different persons and in the same person from time to time. The temporary loss is not limited to the immediate region of the fatiguing tone, but is widespread at and above that tone. No losses were found below the fatiguing tone. Recovery rates also were found to be variable. In those with perceptive hearing losses, no tendency to be unduly susceptible to auditory fatigue was found, so that it is not necessarily true that exposure to noise will cause a rapid progression of the loss already present. After the subject has been flying the hearing loss tends to be spread over the whole auditory spectrum, but with a peak at about 2,048 cycles. In those with a severe "V"-notch in their chart, prior to flight, the loss after exposure to the noise of flight was observed throughout the tone scale. To determine whether hearing losses occurring after exposure to aircraft noise are permanent or not 100 cadets were selected for study. Audiograms were made before and after three periods of training. A few hours after the first daily flight exercises 19% showed a loss of fifteen decibels or more, especially about 2,896, 4,096 and 5,792 cycles. After an additional seventy hours of flight there was a real tendency for ears which showed losses after the first period to regain that hearing, in spite of the continued exposure to aircraft noise. Forty of the same subjects were further tested after a third seventy hours of flying. These were allowed twenty-four hours or more of rest before repetitive audiograms were made. A small number showed a slightly increased "V"-notching. In none was there a loss which interfered with the hearing of speech.

Acetylsalicylic Acid: A Probable Cause for Secondary Post-Tonsillectomy Hæmorrhage.

RUDOLPH SINGER (*Archives of Otolaryngology*, July, 1945) states that the incidence of secondary hæmorrhage of the type occurring on the sixth, seventh or eighth day after tonsillectomy is negligible in the hospitals of Central Europe. Since the operative techniques are much the same as those employed elsewhere, it appears clear that the difference in the post-operative course is due to some other factor. Only one significant factor has been found. That is the administration of acetylsalicylic acid to relieve pain; in Central Europe aminopyrine is used instead. The author in 1943 observed 75 patients to whom no acetylsalicylic acid was given. There was no secondary hæmorrhage in this series. Reference is made to laboratory workers who have shown that salicylic acid and some of its derivatives when administered in conjunction with a diet deficient in vitamin *K* can cause prothrombinopenia. If vitamin *K* was administered simultaneously prothrombinopenia did not occur.

Treatment of External Otitis.

JOSEPH GOLDSTEIN (*Archives of Otolaryngology*, August, 1945) states that in the treatment of external otitis a solution is made by dissolving one chlorazine (chloramine, United States Pharmacopœia) tablet in one ounce of tepid water. With the use of an ordinary medicine dropper the auditory canal is flushed by filling and withdrawing the liquid until the fluid returns clear, after which the canal is dried. Liquid petrolatum may be applied to excoriated skin. The process is repeated on alternate days, the course usually taking about ten days. The canal is then swabbed over with a solution of metacresylacetate (cresatin), to which 1% of thymol has been added. There is no discomfort during treatment and itching ceases after a few days.

British Medical Association News.

NOTICE.

THE General Secretary of the Federal Council of the British Medical Association in Australia has announced that the following medical practitioners have been released from full-time duty with His Majesty's Forces and have resumed civil practice as from the dates mentioned:

Dr. W. F. L. Liggins, 25, Frenchman's Road, Randwick (April 22, 1946).
Dr. J. G. Radford, 195, Malabar Road, Coogee, and 25, Frenchman's Road, Randwick (April 22, 1946).
Dr. T. Rose, 77, Old South Head Road, Bondi Junction (May 1, 1946).

Medical Societies.

MELBOURNE PÆDIATRIC SOCIETY.

A MEETING of the Melbourne Pædiatric Society was held on September 12, 1945, at the Children's Hospital, Carlton, Melbourne, DR. ROBERT SOUTHBY, the Acting Chairman, in the chair.

Fœtal Erythroblastosis.

DR. KATE CAMPBELL read a paper on "Clinical Aspects of Fœtal Erythroblastosis" (see page 686).

DR. REGINALD WEBSTER said that, as judged by the attendance, it was a happy suggestion that a meeting of the society should provide for a discussion of erythroblastosis, or as it was more accurately described, congenital hæmolytic anæmia. Interest in the subject had been stimulated the world over by the illuminating researches which had revealed the fundamental role of iso-immunization in the ætiology of the disease, and if the rapid growth of a literature of already encyclopædic dimensions was any guide, penicillin itself had not exceeded the Rh factor in appeal to the imagination. Dr. Campbell had introduced the subject very ably, and it was his problem to select points for profitable discussion and deal with them within a reasonable time limit.

Dr. Webster said that it had occurred to him that in the first place he might review the sequence of pathological processes and their interactions in perhaps a little more detail than the necessity to cover a much wider field had permitted Dr. Campbell to do. There was now general agreement that the source from which all evils flowed was an abnormal and excessive destruction of fœtal red blood cells by immune antibodies, which were demonstrable as agglutinins *in vitro*, although they acted as hæmolysins *in vivo*. It was remarkable that this should be so, and that not even the addition of fresh complement would induce Rh antibodies to proceed in the test tube beyond the stage of agglutination of red cells to that of hæmolysis. On the destruction of red cells, there inevitably ensued hæmolytic anæmia, of which there were three conspicuous results: (i) anoxæmia, inseparable from the reduced oxygen-carrying capacity of the depleted red blood corpuscles; (ii) hæmolytic icterus, referable to the liberation of an unduly large amount of hæmoglobin and its conversion into bilirubin; (iii) erythroblastæmia, the appearance of variable numbers—sometimes incredibly large—of immature red cells in the peripheral blood, derived from extramedullary foci of erythropoiesis in liver, spleen, and other organs where hæmatogenetic centres normal to fœtal life maintained their activity after birth in an endeavour to compensate for the exaggerated destruction of red cells. The next phase was liver damage, brought about by three factors. The first was the crowding of the liver sinusoids with erythroblasts, to the compression and embarrassment of the polygonal glandular cells of the hepatic parenchyma. Also to be considered was the deposition of hæmosiderin in the liver cells, and the third factor leading to impaired hepatic function was the deterioration in the endothelium of the bile capillaries occasioned by anoxæmia.

Dr. Webster went on to say that undermined liver function manifested itself in three ways, and its first expression was hypoproteinæmia, the maintenance of blood proteins being an important function of the liver. The second indication was jaundice, damaged liver cells being inefficient in secreting (or excreting) and transmitting to the bile capillaries the bilirubin, "processed" by the Kupffer cells from the abounding free hæmoglobin. In the third place the macrocytosis known to be associated with liver damage was present in erythroblastosis, and macrocytes, like nucleated red cells, compared badly with normocytes as oxygen carriers and contributed to anoxæmia.

Dr. Webster said that it would now have become evident that anoxæmia derived from three sources, hæmolytic anæmia, erythroblastæmia and macrocytosis, and that it led to endothelial damage, at the door of which were to be laid the following three types of pathological change: (i) œdema, in the production of which endothelial damage was linked with hypoproteinæmia; (ii) purpura—a not infrequent occurrence in congenital hæmolytic anæmia (at the last meeting of the society he had shown a pair of grossly hæmorrhagic adrenal glands as illustrative of the purpuric tendency in erythroblastosis); (iii) damage to endothelial lining of bile capillaries, with which had to be considered stasis of bile due to hepato-cellular jaundice. Bile stasis promoted the formation of bile plugs and the introduction of an element of obstructive jaundice, the outward and visible sign of the summation of these changes being *icterus gravis*.

Dr. Webster acknowledged that, in presenting the various interdependent and interacting factors in the pathogenesis of congenital hæmolytic anæmia, he had drawn largely upon an article by I. Davidsohn, which appeared in the *Medical Clinics of North America*. It had occurred to him that the substance might be well remembered by application of the "rule of three". It might have been noted that there were three results of hæmolytic anæmia, three factors inducing liver damage, three manifestations of impaired liver function, three sources of anoxæmia, and three types of change supervening on endothelial damage. With regard to diagnosis, he would say, "put not your trust in erythroblastæmia", which was an inconstant phenomenon; there might be no nucleated red cells in the blood stream at birth, and erythroblastæmia might not occur in congenital hæmolytic anæmia until after recovery had begun. On the other hand, the blood of the healthy newborn infant sometimes contained so many erythroblasts as to appear abnormal. Turning to the Rh factor, Dr. Webster emphasized that a demonstration that the mother was Rh-negative and father and baby both Rh-positive was not of itself sufficient basis for a diagnosis of erythroblastosis; it showed no more than that what he might term the necessary Rh potential existed. It was to be remembered that the fœtus was affected with congenital hæmolytic anæmia in only one in forty pregnancies in which conditions permitting iso-immunization obtained. A well-founded clinical diagnosis was supported by such a finding and further buttressed by the detection of anti-Rh agglutinins in the serum of the mother and possibly in that of the baby. In 90% of pregnancies the issue of which was the birth of an erythroblastotic baby, the mother's red cells lacked the Rh antigen while those of father and baby possessed it. Anti-Rh agglutinins were demonstrable in the mother's serum with a frequency with regard to which varying results had been obtained by different workers; but all were agreed that not uncommonly such agglutinins could not be detected. Agglutinins might not be demonstrable at any stage, or after being absent at the time of delivery they might appear within a period of seven to twenty-one days after birth. This mystifying observation, as also the equally puzzling fact that the concentration of agglutinins in the mother's serum bore no relation to the severity of the disease in the infant, seemed to have been elucidated by Wiener's demonstration of a second Rh iso-antibody, which he had termed the "blocking antibody". In the problem presented by many Rh-negative patients, who were undoubtedly sensitized to the Rh factor, but in whose plasma agglutinins could not be demonstrated, it occurred to Wiener that antibodies might still be present and capable of combining with Rh-positive red cells, but incapable of agglutinating them. The idea was subjected to experimental trial by the exposure of highly agglutinable Rh-positive test cells to the action of apparently inert serum obtained from the mothers of erythroblastotic babies. When after such exposure an active anti-Rh serum was added, it was found that the test cells were no longer agglutinable; evidently the action of the active agglutinin had been "blocked". The serum of a number of patients with erythroblastotic babies, when the usual tests for anti-Rh agglutinin had been unsuccessful, was examined in this manner, and in most instances clean-cut blocking reactions were obtained; these indicated the presence of a special sort of anti-Rh iso-antibody. Steps were taken to show that the reaction was specific, and that the effect of the blocking antibody was obtainable only with serum from Rh-negative subjects sensitized to the Rh factor.

Dr. Webster suggested that the appearance of anti-Rh agglutinin for the first time in the serum of a woman a few days after delivery was explicable on the basis of a more rapid decline in the titre of the blocking antibody than in that of the agglutinin. When the blocking antibody dropped out of the competition for sites of occupation on the red cells, the agglutinin came into its own. Wiener had even suggested that of the two sorts of Rh antibody, the blocking antibody might eventually prove of the greater clinical significance. At all events, in all matters pertaining to the Rh factor A. S. Wiener spoke with authority, and his work had furnished an attractive explanation of the apparently incongruous lack of correlation between the titre of anti-Rh agglutinins in the maternal serum and the severity of the disease in the infant. It was interesting to examine the minority (10%) of cases in which the mother was Rh-positive; in these it would seem that some red cell antigen other than Rh, such as A, B, O, M, N, or P must be provocative of iso-immunization. Of the agglutinins to these several antigens, only anti-A and anti-B occurred regularly in human serum under normal conditions, and there was evidence that their strength might be increased in a woman bearing a fœtus containing the appropriate antigen. The natural anti-A or anti-B agglutinins of a woman of blood group O, for instance, might acquire an enhanced titre should she become pregnant with a fœtus of blood group A or blood group B respectively. Boorman, Dodd and Mollison had reported titres of 1:3,200 and 1:8,000,000 for anti-B agglutinins in two Rh-positive mothers of erythroblastotic infants. It was to be noted that they had also observed titres of 1:3,200 in women bearing normal children. Iso-immunization due to the incompatibility in the ABO grouping of the so-called heterospecific pregnancy was said to be more prone to occur when the fœtus was a "non-secretor", and it had interested him to learn from Dr. Campbell that the view was now being advanced that "secretors" were more potent in this connexion than "non-secretors". One subject in five was a "non-secretor", and such description applied to persons in whom the A and B antigens resembled the Rh factor in being largely retained in the tissues, rather than circulating freely in the bodily fluids; in the latter case they served as a store of extracorpuscular, mobilized antigen, available to take the shock of trans-placental agglutinins and thus protect the red cells. It would appear that heterospecific pregnancy with respect to the ABO groups but rarely resulted in erythroblastosis in the infant, and the disease might be assigned to this cause only when a positive diagnosis could be made and the possibility of immunization to any other antigen definitely excluded.

Dr. Webster went on to say that the fact that a woman was Rh-positive afforded her no absolute guarantee that trouble due to iso-immunization would not arise. At the last meeting of the society he had reported two instances of *icterus gravis*, in which the respective mothers and infants were both Rh-positive and of the same ABO grouping. The most probable explanation that he could advance for such occurrences was that they depended on differences in the Rh subtypes of mother and baby; there was, of course, the possibility that some irregular agglutinin was involved, such as anti-Hr, to which he would return later. The work of Davidsohn and Toharsky had strongly suggested, and that of Wiener had finally determined, that the Rh factor was not a single uniform antigen, but a complex of several fractions which presented themselves in varying combinations. In addition to three anti-Rh agglutinins, Wiener had identified five Rh agglutinogens and had shown that the agglutinogens combined in such a way as to produce eight different blood types, if the Rh-negative type was included. If a mother lacked a component of the Rh complex which the baby possessed, she, although Rh-positive, was susceptible to iso-immunization by the fraction in which she was deficient. The operation of Rh subtypes was well illustrated in a case reported in THE MEDICAL JOURNAL OF AUSTRALIA of April 21, 1945, by R. T. Simmons and G. A. Kelsall. Dr. Webster said that the intensive study of iso-immunization in relation to erythroblastosis during recent years had shown that the disease might appear in circumstances in which the usual relation of Rh-negative mother and Rh-positive infant was reversed. Because of this reversal, the agglutinin concerned had been named anti-Hr. This agglutinin clumped the red cells of all Rh-negative persons and those of many Rh-positive persons. It appeared to be an antibody to the Rh-negative factor, which many workers considered should be regarded as something more than an absence of Rh and not entirely inert. Some workers had noted an unusually high proportion of Rh-negative men among the husbands of Rh-positive mothers with affected children, and it might be that the anti-Hr factor frequently operated in the case of an Rh-positive mother. To produce anti-Hr, however, it was not necessary that the father should be Rh-negative; it might still arise when both father and baby were Rh-positive. The introduction of anti-Hr led naturally to consideration of that other remarkable agglutinin of Race and Taylor, named by them St, and distinguished by its agglutinating the red cells of all Rh-negative (rhrh) and of all heterozygous Rh-positive (Rhrh) persons; indeed, St serum had been found to agglutinate the red blood cells of all but about 20% of the population, all of which St-negative subjects must therefore be homozygous. They actually represented about half the Rh-positive homozygotes (RhRh). It might be stated that once the disease had appeared, the mother's only hope of a normal child lay in her bearing an Rh-negative baby. This hope would not be realized if the father was homozygous. Should he be heterozygous, the best prospect that could be offered was that the next child had an even chance of escaping the disease. By the use of their St serum and other advanced technique, Race and Taylor had shown that it was possible to determine serologically the genotype of approximately 75% of Rh-positive people, and unless it could be proved in this way, or by his having an Rh-negative child or an Rh-negative parent, that the father was heterozygous, the outlook was very unfavourable. In conclusion, Dr. Webster said that he was conscious of having traversed aspects of the subjects already covered by Dr. Campbell, but had he not done so, Dr. Campbell's very comprehensive paper would have left him with nothing to say. In such an intricate subject there was perhaps some advantage in the reiteration of certain points. To appreciate the significance of the Rh factor and follow developments in relevant research, it was necessary to acquire the vocabulary and learn the language. He hoped that the meeting had not been confused by the serological nomenclature and that he had succeeded in initiating discussion on a plane worthy of Dr. Campbell's excellent paper.

DR. JOHN GREEN congratulated Dr. Campbell on her paper. He said that he was amazed that Dr. Webster could unerringly traverse the intricate pathways travelled by Dr. Campbell. He noted an invitation for free discussion at the bottom of the agenda paper, but admitted that he felt a little out of his depth. However, his clinical interest had been aroused, and he believed that he had been concerned with one of the earliest cases in Melbourne. The mother concerned had given birth to four stillborn babies. Dr. Green said that a point which exercised the mind of the obstetrician was whether to induce labour early in these cases; he could not elucidate this matter. In one family he recalled, the first baby was normal, the second baby died *in utero*, and in the third pregnancy labour was induced early. The baby became heavily jaundiced soon after birth and survived; but at eight months the child had a peculiar appearance and the ultimate prognosis was uncertain. In another case in which two previous pregnancies had ended with death *in utero*, and in which labour was induced one month before the appointed time, a normal child resulted whose blood proved to be Rh-negative. Dr. Green said that in some cases jaundice came on dramatically, and this applied also to anæmia. In this respect he could recall a baby who appeared quite well on the seventh day and who was suffering from shock and obviously very ill on the eighth day. Investigation had revealed Rh incompatibility, and a blood transfusion was given with a good result. Dr. Green went on to say that in two out of three or three out of four cases the first-born escaped the disease, so that the only hope of a homozygous father was his first baby. In such cases Dr. Green had observed that babies had been lost by accidental hæmorrhage, a macerated fœtus resulting. He had also noted that vitamin *K* had been given by accident to one patient with apparently good effect. It was just possible that this vitamin played a part in placental permeability and offered some hope to parents with this unfortunate blood incompatibility.

DR. JOHN MCLEAN said that he was glad to have the opportunity of hearing Dr. Campbell's paper. He had looked through his own records dealing with such cases and had found that he had given transfusions of Rh-negative blood to ten erythroblastotic babies, in all cases by the direct method. Six had been given one transfusion and four had been given two or more transfusions. The average amount of blood given was three and a half ounces. All the babies recovered from the immediate condition, except one, which was premature and was given an exsanguination transfusion. The baby died of bronchopneumonia. Another baby died from a septic condition after three or four months. Dr. McLean wondered whether Dr. Campbell thought whole blood to be preferable to citrated blood in these cases.

DR. JEAN MACNAMARA thanked Dr. Campbell for her paper and Dr. Webster for his comments. She was anxious to learn whether such blood incompatibility occurred in animals. She also asked for guidance and advice concerning the usefulness of tests for such blood incompatibilities in the group of children labelled "spastic" or just "a bit queer". There had been a considerable increase in the incidence of such cases appearing under various guises, such as athetosis, spasticity *et cetera*. Some of these apparently fell into the post-rubella group. In others, a story of some jaundice soon after birth was obtained and blood incompatibility was demonstrable. Dr. Macnamara asked whether any tests were available to prove the presence of this disease in older children, and whether there was anything more than presumptive evidence that the child's cerebral damage was due to this cause.

DR. HUBERT SMITH said that blood transfusion was only substitution therapy, and some babies would die. He was puzzled as to the cause of death in such cases. He wondered whether liver failure was to blame if hæmolytic anæmia was not the cause.

DR. LUCY BRYCE said that Dr. Levinson insisted on carefully questioning women who had had previous blood transfusions. She had encountered cases in which a preceding blood transfusion had resulted in an adverse reaction in the first pregnancy. Another category in which the first pregnancy might be affected was when there was incompatibility in the ABO grouping of the parents and their offspring. Another point of practical importance was to assess the chances of an Rh-negative offspring resulting from incompatible parents. This, of course, depended on demonstrating that the father was heterozygous. This decision could be arrived at with a complete range of testing serum. Other living children might give the clue—for example, the first-born child might be Rh-negative. This might be simpler than searching for grandparents.

DR. G. ANDERSON asked whether any explanation was available for the fact that the baby's own red cells were hæmolysed by the giving of a blood transfusion, as was shown by the fall in the number of red cells after certain transfusions.

DR. ROBERT SOUTHBY said that he had seen the baby referred to by Dr. Green after labour had been induced at eight months. The baby became quickly jaundiced. After a blood transfusion, temporary improvement set in. A second transfusion was given after an interval of three days. However, the baby's condition continued to deteriorate. When the baby's blood was investigated at this stage, it had only Rh-negative red cells and appeared to be drifting into an aplastic type of anæmia. However, after a third transfusion the child's condition improved. Jaundice disappeared at six weeks. The baby was now aged twelve months and was exhibiting the characteristics of kernicterus. It was spastic and mentally retarded. Dr. Southby said that another interesting family group was one in which the first pregnancy terminated at eight months in a premature baby who thrived well but later developed epilepsy. The second child was also born at eight months. It was microcephalic and "spastic". The third pregnancy also terminated spontaneously at eight months. Rh testing showed the mother to be Rh-negative and the baby Rh-positive, and the three appeared to fit into the Rh incompatibility group. Dr. Southby said that he had allowed the mother to feed all the babies at the breast, which she did with success. All the babies thrived well and no clinical upsets were seen. Dr. Southby commended Dr. Campbell for her warning against aspiration of the sagittal sinus for collecting a sample of blood from jaundiced babies. He recalled two babies who had died after this procedure.

Dr. Campbell, in reply, thanked the various speakers for contributing to the discussion, especially Dr. Webster. In answer to Dr. McLean's question, she said that she noted no difference when using whole blood and citrated blood. She remembered one baby who had received transfusions of both kinds of blood at intervals without any difference in the result. Dr. Campbell, in answer to Dr. Green's query, said that she had no experience of the influence of vitamin *K* on the permeability of the placental capillaries. As to the cause of death which puzzled Dr. Smith, she could only say that all the organs were spoilt and it was difficult to lay the blame on any one organ. In fulminating cases, one was usually struck by the intense yellow change seen in the brain. Dr. Campbell said that she thought that there was a big field for research in the group of "spastics" referred to by Dr. Macnamara. Similar subjects in mental institutions were being investigated by American workers. The diagnosis was not easy in late cases. No antibodies would be demonstrable in the mother's blood after ten years. It would be necessary to make a decision on the mother's blood group and that of the unaffected children. In the cases mentioned by Dr. Anderson, Dr. Campbell suggested that a fall in the number of red cells of the recipient might have occurred in any case, or possibly toxins were liberated by hæmolysis occurring in the donor's corpuscles.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 78, of April 26, 1946.

PERMANENT NAVAL FORCES OF THE COMMONWEALTH (SEA-GOING FORCES).

Promotion.—Surgeon Captain William James Carr, C.B.E., is promoted to the rank of Surgeon Rear-Admiral, dated 7th March, 1946.

Transfer to the Retired List.—Surgeon Rear-Admiral William James Carr, C.B.E., is transferred to the Retired List, dated 8th March, 1946.

AUSTRALIAN MILITARY FORCES.

Australian Army Medical Corps.

WX1546 Colonel (Temporary Brigadier) G. B. G. Maitland, D.S.O., D.C.M., from Director of Medical Services Headquarters First Australian Army (Australian Imperial Force) is appointed Deputy Director-General of Medical Services "A" Branch Headquarters Australian Military Forces, 28th February, 1946.

NX102477 Lieutenant-Colonel K. A. McGarrity is appointed to command 103rd Australian Convalescent Depot, 13th February, 1946.

QX6439 Lieutenant-Colonel N. H. Morgan relinquishes command of 2nd/12th Australian Field Ambulance, 8th February, 1946.

NX439 Colonel (Temporary Brigadier) W. P. MacCallum, D.S.O., M.C., relinquishes the appointment of Deputy Director-General of Medical Services "A" Branch Headquarters Australian Army Military Forces and is placed upon the Regimental Supernumerary List, 28th February, 1946.

NX114319 Lieutenant-Colonel (Temporary Colonel) S. C. M. Hiatt relinquishes the appointment of Assistant Director of Medical Services Headquarters, 3rd Australian Division (Australian Imperial Force), and is placed upon the Regimental Supernumerary List, 8th February, 1946.

NX108462 Lieutenant-Colonel S. D. Mears relinquishes command of 103rd Australian Convalescent Depot and is placed upon the Regimental Supernumerary List, 13th February, 1946.

NX141960 Captain J. McB. White is seconded 3rd January, 1946.

NX70384 Captain V. M. Putland ceases to be seconded, 14th December, 1945.

NX12301 Captain A. G. C. Budge ceases to be seconded and is placed upon the Regimental Supernumerary List, 14th December, 1945.

The following officers are placed upon the Regimental Supernumerary List: VX14795 Lieutenant-Colonel D. O. Brown and QX40819 Major W. V. Connor, 8th February, 1946. Majors (Temporary Lieutenant-Colonels) VX108422 R. J. Farnbach, 13th February, 1946, and NX70332 E. H. Goulston, 4th February, 1946.

QX6071 Colonel K. B. Fraser, E.D., relinquishes the appointment of Deputy Director of Medical Services Headquarters, Queensland Lines of Communication Area, and is transferred to the Reserve of Officers (Australian Army Medical Corps), 15th February, 1946.

QX6493 Lieutenant-Colonel (Temporary Colonel) F. G. Scoles, E.D., relinquishes the rank of Temporary Colonel and is transferred to the Reserve of Officers (Australian Army Medical Corps) with the rank of Lieutenant-Colonel and is granted the rank of Honorary Colonel, 7th February, 1946.

QX6276 Lieutenant-Colonel D. McR. Yeates is transferred to the Reserve of Officers (Australian Army Medical Corps), 30th January, 1946.

To be Temporary Colonel, 21st December, 1945.—VX111102 Lieutenant-Colonel D. Zacharin.

To be Temporary Lieutenant-Colonels.—Majors NX130933 T. W. Freeman, 4th February, 1946, and VX133459 H. E. Pearce, 13th February, 1946.

To be Lieutenant-Colonel, 27th September, 1945.—VX14795 Major (Temporary Lieutenant-Colonel) D. O. Brown.

No. 102 (*Holland Park*) *Military Hospital.*—NX108463 Major F. H. McC. Callow is removed from the Regimental Supernumerary List, 23rd January, 1946.

No. 115 (*Heidelberg*) *Military Hospital: To be Captain* (*Temporary Major*), *21st December,* 1945.—VX98459 John Matthias Joseph Jens.

118*th Australian General Hospital* (*Australian Imperial Force*).—Q273987 Captain L. I. Burt is transferred from Australian Army Medical Corps (Medical) Reinforcements with regimental seniority as from date of transfer, 11th January, 1946.

2*nd*/2*nd Australian Casualty Clearing Station.*—NX170034 Captain J. V. Sanders is placed upon the Regimental Supernumerary List, 25th December, 1945.

104*th Australian Casualty Clearing Station* (*Australian Imperial Force*).—SX27742 Major R. N. C. Bickford is removed from the Regimental Supernumerary List, 23rd January, 1946.

WX33057 Lieutenant-Colonel (Temporary Colonel) E. J. T. Thompson, M.C., E.D., from Deputy Director of Medical Services, Headquarters, Northern Territory Force (Australian Imperial Force), is appointed Assistant Director, Medical Services, Headquarters, 11th Australian Division (Australian Imperial Force), 23rd January, 1946.

VX48626 Lieutenant-Colonel A. C. Mendelsohn relinquishes command of 2nd/15th Australian Field Ambulance, and is appointed to command 2nd Australian Field Ambulance, 21st January, 1946.

VX39316 Major H. L. Andrews is transferred from the Permanent Supernumerary List (Australian Army Medical Corps), and is appointed to command 107th Australian Convalescent Depot, 21st January, 1946.

NX70413 Lieutenant-Colonel (Temporary Colonel) N. D. Barton, C.B.E., E.D., relinquishes the appointment of Deputy Director of Medical Services, Headquarters, Morotai Force, and is placed upon the Regimental Supernumerary List, 21st January, 1946.

VX14380 Lieutenant-Colonel (Temporary Colonel) C. W. B. Littlejohn, O.B.E., M.C., relinquishes the appointment of Consultant Surgeon, "A" Branch, Headquarters, Australian Military Forces, and is placed upon the Regimental Supernumerary List, 30th January, 1946.

NX103436 Lieutenant-Colonel A. H. Gee relinquishes command of 4th Australian Field Ambulance, and is placed upon the Regimental Supernumerary List, 23rd January, 1946.

NX123664 Lieutenant-Colonel K. C. T. Rawle relinquishes command of 104th Australian Casualty Clearing Station, and is placed upon the Regimental Supernumerary List, 23rd January, 1946.

SX1463 Lieutenant-Colonel S. J. Douglas relinquishes command of 2nd/11th Australian Field Ambulance, and is placed upon the Regimental Supernumerary List, 21st November, 1945.

NX70833 Lieutenant-Colonel A. D. Frost relinquishes command of 2nd/3rd Australian Field Ambulance, and is placed upon the Regimental Supernumerary List, 23rd January, 1946.

NX128008 Major (Temporary Lieutenant-Colonel) L. P. Hiatt relinquishes command of 2nd Australian Field Ambulance, and is placed upon the Regimental Supernumerary List, 21st January, 1946.

The following officers are placed upon the Regimental Supernumerary List: NX77303 Captain (Temporary Major) J. A. Paul and NX146280 Captain J. F. McInerney, 6th January, 1946, VX199 Lieutenant-Colonel E. S. J. King, 30th January, 1946, and P390 Captain G. H. Vernon, M.C., 18th January, 1946.

SX1472 Colonel (Temporary Brigadier) D. M. Salter relinquishes the rank of Temporary Brigadier, and is transferred to the Reserve of Officers (Australian Army Medical Corps), with the rank of Colonel, and is granted the rank of Honorary Brigadier, 17th November, 1945.

The following officers relinquish the rank of Temporary Colonel, and are transferred to the Reserve of Officers (Australian Army Medical Corps), with the rank of Lieutenant-Colonel, and are granted the rank of Honorary Colonel: Lieutenant-Colonels (Temporary Colonels) NX35131 A. W. Morrow, D.S.O., 23rd November, 1945, NX13 R. H. Macdonald, O.B.E., 3rd January, 1946, VX154 W. W. Lempriere, D.S.O., 24th January, 1946, and QX6247 D. A. Cameron, 5th December, 1945.

QX42595 Major (Temporary Lieutenant-Colonel) N. M. Gutteridge, E.D., relinquishes the rank of Temporary Lieutenant-Colonel, and is transferred to the Reserve of Officers (Australian Army Medical Corps), with the rank of Major, and is granted the rank of Honorary Lieutenant-Colonel, 19th January, 1946.

The following officers are transferred to the Reserve of Officers (Australian Army Medical Corps): Lieutenant-Colonels SX1463 S. J. Douglas, 13th December, 1945, NX34895 W. Freeborn, M.M., and VX47578 J. E. Clark and SX1467 G. T. Gibson, 15th January, 1946, QX6069 H. R. Love, 16th January, 1946, WX1524 R. W. Johnson, 17th January, 1946, VX34848 I. A. Brodziak, 30th October, 1945, QX6083 J. J. Ryan, M.C., 8th January, 1946, SX1471 N. P. Wilson, 10th January, 1946, SX2816 J. M. Bonnin, 19th January, 1946, NX34745 J. C. English, 4th January, 1946, and VX222 L. E. Rothstadt, 19th January, 1946.

SX1465 Lieutenant-Colonel H. C. Nott is placed upon the Retired List, 8th January, 1946.

To be Temporary Lieutenant-Colonel, 7th November, 1945.—VX51843 Major K. B. Brown.

To be Lieutenant-Colonel, 27th September, 1945.—NX70833 Major (Temporary Lieutenant-Colonel) A. D. Frost.

118*th Australian General Hospital* (*Australian Imperial Force*).—TX6261 Captain J. D. Trembath is placed upon the Regimental Supernumerary List, 20th January, 1946.

126*th Australian Special Hospital.*—N429481 Captain E. L. B. Hanrahan is removed from the Regimental Supernumerary List, 11th January, 1946.

VX39316 Major H. L. Andrews is transferred to Australian Army Medical Corps (Medical), 21st January, 1946.

Reserve of Officers.

The undermentioned officers are transferred to the Reserve of Officers with effect from the dates indicated, and where applicable cease to be seconded. Officers holding temporary rank relinquish such temporary rank on the date of transfer to the Reserve of Officers:

Majors NX76365 T. K. S. Whiting, 10th January, 1946, VX39184 H. Shannon, 19th January, 1946, NX34955 L. J. Cains, 23rd November, 1945, VX239 W. J. L. Duncan, 8th January, 1946, NX34710 G. V. Mutton, 22nd January, 1946, and NX12279 J. F. Sullivan, M.C., 20th December, 1945, Captains VX104251 C. R. Copland, 20th December, 1945, and NX126034 M. W. Matheson, 8th January, 1946.

2*nd*/1*st Australian General Hospital.*—Majors VX39432 D. G. Alsop, 22nd December, 1945, and NF115193 E. F. L. Laurie, 24th January, 1946.

2*nd*/2*nd Australian General Hospital.*—Majors VX133246 A. A. Ferris, 3rd January, 1946, and VX48595 J. McD. Agar, 4th January, 1946.

2*nd*/4*th Australian General Hospital.*—Majors VX111072 K. N. Uhd, 11th December, 1945, VX48401 A. W. M. Hutson, 8th December, 1945, and NX70336 C. S. Colvin, 4th December, 1945.

2*nd*/5*th Australian General Hospital.*—Majors NX70217 R. G. B. Cameron, 24th January, 1946, and VX39117 D. R. Leslie, 22nd January, 1946.

2*nd*/6*th Australian General Hospital.*—Majors VX150045 W. Pook, 15th January, 1946, and NX459 V. G. Bulteau, 16th January, 1946, Captains VX133293 A. E. Alcock, 23rd January, 1946, and NX70403 E. B. Docker, 8th January, 1946.

2*nd*/8*th Australian General Hospital.*—NX70198 Major D. de la F. Henry, 15th January, 1946.

2*nd*/9*th Australian General Hospital.*—NX76501 Major N. J. Clements, 14th December, 1945.

2*nd*/11*th Australian General Hospital.*—VX39304 Major F. W. Farmer, 18th January, 1946.

2*nd*/12*th Australian General Hospital.*—Majors VX58919 F. P. G. Smith, 20th December, 1945, NX70399 P. J. Kenny, 4th January, 1946, and NX355 C. B. Cox, 10th January, 1946.

2*nd*/14*th Australian General Hospital.*—NX70337 Major A. B. Sullivan, 22nd December, 1945.

101*st Australian General Hospital* (*Australian Imperial Force*).—VX138663 Major C. E. Backwell, 20th December, 1945.

No. 102 (*Holland Park*) *Military Hospital.*—VX138582 Major J. F. Williams, 14th December, 1945.

104*th Australian General Hospital.*—N392914 Major V. C. L. Hay, 10th January, 1946.

No. 113 (*Concord*) *Military Hospital.*—NX70261 Major J. Loewenthal, 12th December, 1945.

No. 114 (*Goulburn*) *Military Hospital.*—VX138669 Major H. J. B. Stephens, 18th December, 1945.

No. 115 (*Heidelberg*) *Military Hospital.*—NX34900 Major W. K. Myers, 8th January, 1946, Captains VX66980 E. J. McDonald, 15th January, 1946, and VX55016 N. F. Laidlaw, 5th January, 1946.

116*th Australian General Hospital.*—N393256 Major J. Byrne, 15th January, 1946.

20*th Australian Camp Hospital.*—V147738 Captain E. W. Hands, 12th January, 1946.

70*th Australian Camp Hospital.*—VX39427 Major D. L. G. Thomas, 10th January, 1946.

113*th Australian Convalescent Depot* (*Australian Imperial Force*).—NX149595 Major N. M. Stewart, 17th January, 1946.

115*th Australian Convalescent Depot* (*Australian Imperial Force*).—NX122807 Captain (Temporary Major) H. J. Solomon, 21st December, 1945.

1*st Australian Outpatients' Depot*.—N393024 Captain A. W. Dean, 19th December, 1945.

102*nd Australian Casualty Clearing Station* (*Australian Imperial Force*).—Majors NX107907 R. C. Scobie, 24th January, 1946, and SX10449 J. M. Pedler, 22nd January, 1946.

109*th Australian Casualty Clearing Station* (*Australian Imperial Force*).—NX76300 Major B. R. Morey, 14th December, 1945.

2*nd/1st Australian Field Ambulance*.—NX77250 Major I. W. MacNaught, 18th December, 1945.

2*nd/5th Australian Field Ambulance*.—VX39414 Major V. E. Sampson, M.C., 3rd January, 1946.

2*nd Australian Field Ambulance* (*Australian Imperial Force*).—NX70277 Major A. M. Barron, 5th January, 1946.

15*th Australian Field Ambulance* (*Australian Imperial Force*).—VX81139 Major M. O. K. Hughes, 22nd January, 1946.

1*st Australian Army Medical Corps Company* (*Beach Group*) (*Australian Imperial Force*).—VX8304 Major A. H. McGregor, 5th December, 1945.

Intermediate Service Medical Wing Demobilization Centres (*Australian Military Forces Component*).—Majors NX70631 T. J. Ritchie, 22nd December, 1945, NX34995 L. A. Atkins, 19th December, 1945, and NX402 K. J. Friend, 4th January, 1946, Captains NX70923 K. S. Wallace and NX144766 J. F. Boag, 19th December, 1945, and NX113212 K. P. Clifford, 5th January, 1946, Majors VX39239 C. E. Sawrey, 28th November, 1945, and VX39061 G. C. Love, 7th December, 1945, Captains VX58814 R. Kiel, 19th January, 1946, and SX22156 E. H. Levy, 24th January, 1946.

Majors VX47449 B. H. Anderson, 5th December, 1945, VX46174 R. B. Maynard, 6th December, 1945, VX66657 H. A. W. Watson, 13th November, 1945, VX45001 J. F. J. Cade, 3rd January, 1946, NX70158 R. E. Maffey, 14th December, 1945, VX39055 H. A. Phillips, 17th January, 1946, VX47129 I. T. Cameron, 19th January, 1946, NX70674 E. A. Marsden, 20th December, 1945, NX76596 C. E. M. Gunther, 13th December, 1945, NX70489 P. F. Murphy, 10th January, 1946, and NX70970 R. Dick, 18th January, 1946, Captains NX35087 F. F. Elliott, 5th December, 1945, NX70273 C. R. B. Richards, 8th December, 1945, NX70385 G. D. Cumming, 12th January, 1946, NX35135 I. L. Duncan, 27th November, 1945, NX34905 R. B. Speirs, 29th November, 1945, VX42739 R. G. M. Forsyth, 15th December, 1945, NX76302 D. C. C. Hinder, 14th December, 1945, VX39223 J. P. Catchlove, 16th January, 1946, NX71143 R. G. V. Parker, 14th December, 1945, and VX61260 E. B. Dreverman, 10th January, 1946, and NX16308 Lieutenant J. G. Kelliher, 8th January, 1946.

WX11064 Major C. R. Dunkley, 8th January, 1946, and VX91683 Captain R. L. J. Park, 27th November, 1945.

2*nd/5th Australian General Hospital*.—QX19064 Major A. F. Quayle, 5th December, 1945.

2*nd/6th Australian General Hospital*.—QX35074 Major D. C. C. Sword, 7th December, 1945.

2*nd/7th Australian General Hospital*.—NX214 Major E. A. Hedberg, 31st October, 1945.

2*nd/9th Australian General Hospital*.—QX25550 Captain C. H. Mansfield, 18th December, 1945.

2*nd/12th Australian General Hospital*.—SX13887 Major R. de G. Burnard, 22nd December, 1945.

No. 102 (*Holland Park*) *Military Hospital*.—QX35076 Captain G. H. Ellis, 4th December, 1945.

103*rd Australian General Hospital*.—QX22736 Major R. V. Rickard, 16th January, 1946.

No. 105 (*Adelaide*) *Military Hospital*.—SX10203 Major F. J. B. Miller and SX13679 Captain A. D. Reid, 4th January, 1946.

No. 112 (*Brisbane*) *Military Hospital*.—QX45908 Captain T. R. Neville, 29th December, 1945.

No. 113 (*Concord*) *Military Hospital*.—VFX92342 Captain M. M. Dixon, 8th January, 1946.

No. 114 (*Goulburn*) *Military Hospital*.—SX10965 Major G. M. Hone, 5th December, 1945.

104*th Australian Casualty Clearing Station* (*Australian Imperial Force*).—WX34977 Major A. D. Smith, 5th January, 1946.

103*rd Australian Mobile Bacteriological Laboratory* (*Australian Imperial Force*).—QX46101 Major A. E. F. Shaw, 14th December, 1945.

Inter-Service Medical Wing Demobilization Centres (*Australian Military Forces Component*).—WX41609 Captain H. J. C. Hanrahan, 27th November, 1945, Q119828 Captain H. Green, 11th December, 1945, VX14488 Major J. Ray, 29th November, 1945, and SX9183 Major P. C. R. Goode, M.C., 30th November, 1945.

Majors VX62081 T. P. Crankshaw, 28th November, 1945, WX11151 A. R. Home, 8th December, 1945, QX22806 B. L. W. Clarke, 19th December, 1945, NX70643 K. J. Fagan, 14th November, 1945, and SX13978 S. Krantz, 11th January, 1946, Captains NX70671 F. H. Mills, 10th November, 1945, VX39258 I. C. Heinz, 9th November, 1945, VX39702 F. J. Cahill, 20th November, 1945, VX39436 V. G. Bristow, 29th November, 1945, QX23518 C. R. Boyce, 12th December, 1945, WX3464 C. L. Anderson, 5th January, 1946, NX35149 R. L. Cahill, 10th November, 1945, VX57546 F. R. Vincent, 21st November, 1945, and VX42738 Lieutenant G. H. Veitch, 29th November, 1945.

Retired List.

The undermentioned officers are placed upon the Retired List on the dates indicated, and, where applicable, cease to be seconded. Officers holding temporary rank relinquish such temporary rank on the date of placement upon the Retired List:

Q40778 Captain C. A. Holmes, 20th November, 1945.

74*th Australian Camp Hospital* (*Australian Imperial Force*).—W38342 Captain J. E. McMahon, 4th December, 1945.

QX19079 Major C. W. Uhr, 6th November, 1945.

Reserve Citizen Military Forces.

Australian Army Medical Corps.

Queensland Lines of Communication Area.—Colonel K. B. Fraser, E.D., is appointed Deputy Director of Medical Services, Queensland Lines of Communication Area (part-time duty), 16th February, 1946.

Post-Graduate Work.

REFRESHER COURSE FOR GENERAL PRACTITIONERS IN MELBOURNE.

THE Melbourne Permanent Post-Graduate Committee has announced the following programme for the refresher course for general practitioners to be held from June 3 to 15, 1946.

Monday, June 3, 1946.—At the Royal Melbourne Hospital: 10 a.m. to 12 noon, Dr. W. A. Hailes, "The Management of Retention of Urine"; 2 p.m. to 4 p.m., Dr. L. Hurley, "Medical Emergencies".

Tuesday, June 4, 1946.—At Saint Vincent's Hospital: 10 a.m. to 12 noon, Dr. H. Mortensen, "Genito-Urinary Problems in General Practice"; 2 p.m. to 4 p.m., Dr. J. Horan, "Gastric Conditions in General Practice".

Wednesday, June 5, 1946.—At the Alfred Hospital: 10 a.m. to 12 noon, Dr. F. Maclure, "Ulcers of the Leg"; 2 p.m. to 4 p.m., Dr. M. C. Davis, "Diagnosis and Treatment in Diseases of the Cardio-vascular System".

Thursday, June 6, 1946.—At the Medical Society Hall, Albert Street: 10 a.m. to 12 noon, Dr. C. H. Dickson, "Legal and Ethical Problems in General Practice". At Saint Vincent's Hospital: 2 p.m. to 4 p.m., Dr. F. May, "Physiotherapy in General Practice".

Friday, June 7, 1946.—At the Royal Melbourne Hospital: 10 a.m. to 12 noon, Dr. B. T. Keon-Cohen, "Common Foot Disabilities"; 2 p.m. to 4 p.m., Dr. E. G. Robertson, "Common Neurological Problems in General Practice".

Saturday, June 8, 1946.—At the Women's Hospital: 10 a.m. to 12 noon, Dr. J. S. Green, "Female Endocrinology in General Practice".

Tuesday, June 11, 1946.—At the Alfred Hospital: 10 a.m. to 12 noon, Dr. C. A. M. Renou, "Fractures of the Upper Limbs"; 2 p.m. to 4 p.m., Dr. E. Downie, "Management of Diabetes in General Practice".

Wednesday, June 12, 1946.—At the Children's Hospital: 10 a.m. to 12 noon, Dr. J. G. Whitaker, "Surgical Treatment of Pyloric Stenosis", "Osteomyelitis in the Newborn"; 2 p.m. to 4 p.m., Dr. J. W. Grieve, "The Non-Thriving Infant".

Thursday, June 13, 1946.—At the Eye and Ear Hospital: 10 a.m. to 12 noon, Dr. Eric Gutteridge, "Ear, Nose and Throat Conditions in General Practice"; 2 p.m. to 4 p.m., Dr. A. S. Anderson, "Eye Conditions in General Practice".

Friday, June 14, 1946.—At the Royal Melbourne Hospital: 10 a.m. to 12 noon, Dr. John Kelly, "Skin Conditions in General Practice". At the Queen's Memorial Infectious Diseases Hospital: 2 p.m. to 4 p.m., Dr. F. V. Scholes, "Infectious Diseases".

Saturday, June 15, 1946.—At the Royal Melbourne Hospital: 10 a.m. to 12 noon, Dr. B. L. Stanton, "Modern Advances in Pharmacology".

In addition opportunity will be given for discussion on problems submitted by those taking part in the course.

Enrolments for this course should be made with the secretary of the committee, College of Surgeons, Spring Street, Melbourne, C.1. (Telephone: JM 1547.)

Correspondence.

THE SPECIAL REPRESENTATIVE MEETING IN LONDON.

SIR: I feel sure that members of the profession in Australia will be interested in the following extract of a letter which I have received from Dr. J. G. Hunter, who is at present in England.

> On Wednesday I attended the representative meeting—and by the way had to say a few words in reply to the welcome of the Chairman of the Representative Body—Dr. J. B. Miller—and also on Thursday. It was a very good meeting and a lengthy one, over 250 notices of motion. Right throughout the meeting, the theme was professional freedom, and if this meeting is indicative of the views of the profession, then they are pretty united. Almost unanimously (and there were about 300 present) they decided: (1) that they would not be directed or controlled, (2) that they would not abandon the right of buying and selling of practices, and (3) that they would not accept salary—in effect that they would not give up their professional freedom. It was good to see the profession take a stand.

Yours, etc.,

HUGH HUNTER,
Assistant Medical Secretary,
British Medical Association,
New South Wales Branch.

135, Macquarie Street,
Sydney,
May 13, 1946.

"ATEBRIN" AND DERMATITIS: AN INQUIRY.

SIR: In reply to "Inquirer" in THE MEDICAL JOURNAL OF AUSTRALIA of April 27, the following may be of interest in regard to the cutaneous manifestations of "Atebrin".

Many drugs are known to produce eruptions on the skin and mucous surfaces of the mouth, so that it is not surprising to find drugs associated with the treatment of malaria, that is, "Atebrin", affecting these sites. Following the use of "Atebrin", there may be a small percentage of cases which show persistent pigmentary changes apart from the yellowish staining. The pigmentation seen in these patients may be diffuse, and cover large areas of the trunk and limbs, or it may occur in patches of irregular size and distribution, or sometimes disseminated like a cutaneous efflorescence. These blackish, slaty-bluish or brownish areas may appear only as a pigmentary change. In some instances the condition may in parts be follicular, or composed of aggregations of small shiny papules resembling *lichen planus*.

As a phase in the pigmentary process, there may be seen an irregular, reticular arrangement not unlike that in *livedo reticularis*. In another phase are to be seen whitish (not atrophic), discrete, circular spots about the size of a pea or a threepenny piece, which become noticeable after raised warty lesions have disappeared.

The face and the greater part of the scalp are amongst the areas least affected. Loss of hair may be a noticeable feature, involving not so much the scalp as the area about the nape of the neck. Likewise the hairs of the axillæ, pubis, body and limbs may be completely or only partially lost. There may be dystrophy; or even loss of the nails on the fingers and toes in severe cases. The tongue may be entirely whitish in colour, simulating a condition seen rarely in *lichen planus*, or there may be whitish spots on the buccal mucosa, also resembling *lichen planus*.

Sweating may be diminished or absent in certain areas. Pruritus is frequently absent.

Recently I saw a patient treated with gold injections who presented a very similar picture to that produced by "Atebrin". The pigmentation only appeared on parts exposed to sunlight following surfing. The area covered by the bathing costume was entirely unaffected. The pigmentation was persistent and similar in colour to that produced by "Atebrin", and covered more or less entirely the exposed surfaces, including the face.

As it very slowly showed some resolution it became reticular in appearance.

There was extensive loss of hair over the scalp, whilst the hair of the axillæ was entirely, and that of the eyebrows partially, lost. There was also cessation of perspiration, and warty growths were in evidence. The patient complained of marked pruritus for some time.

The clinical picture in this case was practically identical with that produced by "Atebrin".

With "Atebrin" sunlight probably also plays a part in determining its appearance, and may account for the protection of the face and portion of the scalp afforded by a hat; whilst other parts of the body remain uncovered.

Yours, etc.,

NORMAN PAUL.

143, Macquarie Street,
Sydney,
May 2, 1946.

PLACENTA PRÆVIA.

SIR: The correspondence on *placenta prævia* in the columns of your journal over the past few weeks provokes me to make one or two comments.

First, Dr. Stephen in his most interesting letter (April 6) quotes the advice of Professor Hart that the patient be examined without gloves because it may be easier to distinguish between blood clot and placenta!

The patient with *placenta prævia* is already a strong candidate for sepsis because of loss of blood and the interference necessary for its prevention or control. To add further to this risk by neglect of an elementary surgical principle (use of rubber gloves) would seem to me incompatible with the major surgical treatment (Cæsarean section) which, I take it, Dr. Stephen would undertake if the examination disclosed a *placenta prævia*. However, I am somewhat relieved to observe that Dr. Stephen does not say that he follows the advice of Professor Hart. I sincerely hope that nobody does, because such a procedure today would be indefensible.

Secondly, while agreeing with the correspondents that Cæsarean section has a place in the treatment of *placenta prævia*, I feel it my duty to curb the surgical enthusiasm which is all too evident today in the management of obstetric abnormalities.

There is a real risk in the advocacy of Cæsarean section for *placenta prævia* without adequate emphasis on the more conservative methods which are still effective in many cases.

Cæsarean section is in itself a severe imposition on the patient; which fact I suggest may not always be sufficiently realized.

In the near future in these columns I anticipate the appearance of an excellent piece of investigation of the blood loss in Cæsarean section which I trust will have a steadying influence on the surgical method of delivery.

Finally, sir, if I may once more refer to Dr. Stephen's letter, I read with interest the account of the patient recently recovered from phthisis, suffering from diabetes and convalescing from pregnancy and Cæsarean section. To leave her bed on the tenth day and push a perambulator to the surgery on the sixteenth is truly a remarkable achievement. It shows what a woman can do, not what she should do.

Yours, etc.,

BRUCE T. MAYES,
Professor of Obstetrics.

University of Sydney,
April 26, 1946.

ULCERS IN THE MOUTH: AN APPEAL FOR HELP.

SIR: A male patient, aged sixty-two years, had a history of indifferent health and persistent ulceration of the mouth and throat of one and a half years' duration. Complete investigation gave negative results. On three occasions he had penicillin lozenges, with slight improvement in his condition the first time. Unfortunately it was not possible to obtain enough lozenges to last over two days. He was given 1,000,000 units of penicillin with improvement in his general condition, and the ulcers cleared up.

Yours, etc.,

F. F. McMAHON.

Main Street,
Lilydale,
Victoria.
April 23, 1946.

Obituary.

GEORGE EDWARD BURDEKIN CLAYTON.

We regret to announce the death of Dr. George Edward Burdekin Clayton, which occurred on April 20, 1946, at Pomona, Queensland.

REDFORD JOHN WRIGHT SMITH.

We regret to announce the death of Dr. Redford John Wright Smith, which occurred on May 5, 1946, at Caulfield, Victoria.

GEORGE ARBUTHNOT VAN SOMEREN.

We regret to announce the death of Dr. George Arbuthnot van Someren, which occurred on May 12, 1946, at Ashfield, New South Wales.

GEORGE ARTHUR BUCHANAN.

We regret to announce the death of Dr. George Arthur Buchanan, which occurred on May 13, 1946, at Manly, New South Wales.

Nominations and Elections.

The undermentioned has applied for election as a member of the Tasmanian Branch of the British Medical Association:

Statham, Cecily Faith, B.A., M.B., B.S., 1946 (Univ. Melbourne), Launceston General Hospital, Launceston.

THE FEDERAL MEDICAL WAR RELIEF FUND.

The following contributions to the Federal Medical War Relief Fund have been received:

Tasmania.

J. S. Reid, £20.
B. Hiller, G. M. W. Clemons, £10 10s.
J. H. B. Walch, H. J. C. Engisch, P. Braithwaite, £5 5s.
R. H. M. Connell, K. Melville Kelly and Jean M. Gunson (joint contribution), £2 2s.
C. I. A. Williams, £1 1s.
Total: £62.

Medical Appointments.

Dr. J. G. Oxley has been appointed Government Medical Officer at Biloela, Queensland.

Dr. G. C. Smith, Director, Division of Industrial Hygiene, Department of Health, New South Wales, has been appointed Deputy Chairman of the Medical Authority in pursuance of section 8 of the *Workmen's Compensation (Broken Hill) Act*, 1920-1945, of New South Wales.

Dr. W. J. Brennan has been appointed a member of an Advisory Committee on Technical Courses at Broken Hill, New South Wales.

Dr. A. N. Kingsbury has been appointed a member of the Food Standards Advisory Committee under the provisions of section 201 of *The Health Act*, 1911-1944, of Western Australia.

Books Received.

"Modern Anæsthetic Practice", edited by the late Sir Humphrey Rolleston, Bt., G.C.V.O., K.C.B., M.D., F.R.C.P., and Alan Moncrieff, M.D., F.R.C.P.; Second Edition; 1946; The Practitioner Handbooks. London: Eyre and Spottiswoode (Publishers) Limited. 8¼" × 5¼", pp. 158, with illustrations. Price: 12s. 6d.

"Atlas of Surgical Approaches to Bones and Joints", by Toufick Nicola, M.D., F.A.C.S., with a foreword by Norman T. Kirk; 1945. New York: The Macmillan Company. Sydney: Angus and Robertson Limited. 11" × 8", with many illustrations. Price: 37s. 6d.

"Micro-Analysis in Medical Biochemistry", by E. J. King, M.A. (McMaster), Ph.D. (Toronto); 1946. London: J. and A. Churchill Limited. 8¼" × 5¼", pp. 176, with 16 illustrations. Price: 10s. 6d.

Diary for the Month.

MAY 21.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAY 22.—Victorian Branch, B.M.A.: Council Meeting.
MAY 23.—New South Wales Branch, B.M.A.: Clinical Meeting.
MAY 24.—Queensland Branch, B.M.A.: Council Meeting.
MAY 28.—New South Wales Branch, B.M.A.: Ethics Committee.
MAY 30.—South Australian Branch, B.M.A.: Council Meeting.
MAY 30.—New South Wales Branch, B.M.A.: Branch Meeting.
JUNE 4.—New South Wales Branch, B.M.A.: Organization and Science Committee.
JUNE 5.—Victorian Branch, B.M.A.: Branch Meeting.
JUNE 5.—Western Australian Branch, B.M.A.: Council Meeting.
JUNE 6.—New South Wales Branch, B.M.A.: Special Groups Committee.
JUNE 7.—Queensland Branch, B.M.A.: Branch Meeting (Bancroft Memorial Lecture).
JUNE 11.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
JUNE 11.—Tasmanian Branch, B.M.A.: Ordinary Meeting.
JUNE 13.—South Australian Branch, B.M.A.: Council Meeting.
JUNE 14.—Queensland Branch, B.M.A.: Council Meeting.
JUNE 18.—New South Wales Branch, B.M.A.: Medical Politics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

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